111-1090 DAC for Pat

#12

PATENT

Attorney Docket No. _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,696,949)
)
Issued: September 29, 1987)
)
To: Reijo J. Toivola, Arto J. Karjalainen, Kauko O.)
A. Kurkela, Marja-Liisa Södervall, Lauri V. M.)
Kangas, Guillermo L. Blanco and Hannu K.)
Sundquist)
)
Assignee: ORION-YHTYMÄ OY)
)
For: NOVEL TRI-PHENYL ALKANE AND ALKENE)
DERIVATIVES AND THEIR PREPARATION)
AND USE)

Assistant Commissioner for Patents
Washington, D.C. 20231

Attention: BOX PATENT EXT

Sir:

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Your applicant, ORION-YHTYMÄ OY, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,696,949 granted to Reijo J. Toivola, Arto J. Karjalainen, Kauko O. A. Kurkela, Marja-Liisa Södervall, Lauri V. M. Kangas, Guillermo L. Blanco, and Hannu K. Sundquist on the 29th day of September, 1987, for NOVEL TRI-PHENYL ALKANE AND ALKENE DERIVATIVES AND THEIR PREPARATION AND USE by virtue of an assignment in favor of ORION-

ORIGINAL

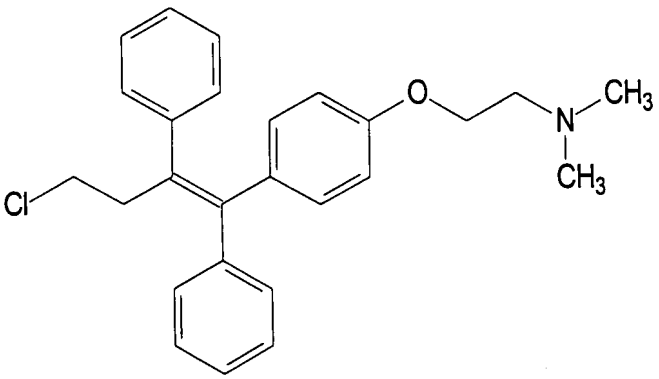
YHTYMÄ OY recorded March 15, 1991, Reel 5635, Frame 0933. By the Power of Attorney enclosed herein (Attachment A), Applicant appoints Ronald J. Kubovcik as attorney for ORION-YHTYMÄ OY with regard to this application for extension of the term of U.S. Patent No. 4,696,949 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Applicant hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. §§ 1.710-1.785). For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format which will follow the requirements of 37 C.F.R. §1.740.

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAMES, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product FARESTON® contains toremifene citrate, chemically described as (Z)-2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-ethanamine citrate; (Z)-4-chloro-1,2-diphenyl-1-[4-[2-(N,N,-dimethylamino)ethoxy]-

phenyl]-1-butene citrate or 2-[p-[(Z)-4-chloro-1,2-diphenyl-1-butenyl]phenoxy]-N,N-dimethylethylamine. Its structural formula is:



•$HOOCCH_2C(OH)(COOH)CH_2COOH$

The Product Information Sheet for FARESTON® is attached hereto as Attachment B (the structural formula for toremifene citrate, not shown on page 1 of the Product Information Sheet corresponds to the above formula).

(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505.

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

The approved product FARESTON® received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act on May 29, 1997 (Attachment C).

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, THE PUBLIC HEALTH SERVICE ACT OR THE VIRUS-SERUM-TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED.

The only active ingredient in FARESTON® is toremifene citrate, which had not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 20-497 by the Food and Drug Administration on May 29, 1997.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO § 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

This Application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. § 1.720(f). The 60 day period in which this application can be submitted will expire on July 27, 1997.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE AND THE DATE OF EXPIRATION:

The complete identification of the patent for which a term extension is being sought is as follows:

Inventors: Reijo J. Toivola, Arto J. Karjalainen, Kauko O. A. Kurkela, Marja-Liisa Södervall, Lauri V. M. Kangas, Guillermo L. Blanco, and Hannu K. Sundquist

Patent Number: 4,696,949

Issue Date: September 29, 1987

Expiration Date: September 29, 2004 (17 years from the date of issue, i.e., September 29, 1987)

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS), AND DRAWINGS:

A true copy of the patent is attached. (Attachment D)

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION CERTIFICATE ISSUED IN THE PATENT:

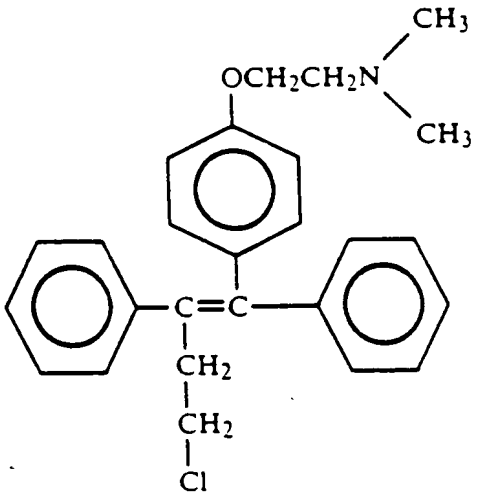
No terminal disclaimer, certificate of correction or reexamination certificate has been issued. A Request for Certificate of Correction was filed on July 8, 1997, to correct the misspelling of the surname of the inventor Hannu K. Sundquist (which appears as

"Sunduiqst" on the patent). Enclosed are copies of the receipts verifying payment of the maintenance fees in 1991 and 1995 (Attachment E).

(9) A STATEMENT THAT THE PATENT CLAIMS, THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH EACH APPLICABLE PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

Claims 1, 2, 3, 4, 5, 6, and 7 of U.S. Patent No. 4,696,949 cover toremifene citrate, the active ingredient in the approved product, a pharmaceutical composition containing toremifene citrate or a method of using toremifene citrate. The applicable claims read on toremifene citrate as follows:

Claim 1: A compound of the formula:



or a non-toxic pharmaceutically acceptable salt or N-oxides thereof.

Toremifene citrate, the active ingredient in FARESTON®, is the non-toxic pharmaceutically acceptable citrate salt of the compound in the structural formula in claim 1.

Claim 2: A compound according to claim 1 which is 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene or a non-toxic pharmaceutically acceptable salt thereof.

Toremifene citrate is the non-toxic pharmaceutically acceptable citrate salt of 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene.

Claim 3: A compound according to claim 1 which is the trans-isomer of 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy] phenyl]-1-butene or a non-toxic pharmaceutically acceptable salt thereof.

Toremifene citrate is the non-toxic pharmaceutically acceptable citrate salt of the trans-isomer of 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene.

Claim 4: A compound according to claim 1 which is the citrate of the trans-isomer of 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene.

Toremifene citrate is the citrate of the trans-isomer of 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene.

Claim 5: A pharmaceutical composition suitable for treating hormone-dependent tumours comprising an anti-tumour effective amount of a compound of claim 1 or a non-toxic pharmaceutically acceptable salt thereof and a compatible pharmaceutically carrier therefor.

Toremifene citrate, which is the non-toxic pharmaceutically acceptable citrate salt of the of the compound in the structural formula of claim 1, is the active ingredient in the approved product FARESTON®. FARESTON® has been approved by the Food and Drug Administration for treatment of metastatic breast cancer in postmenopausal women with estrogen receptor positive or receptor unknown tumors. Refer to the third paragraph of the letter of the Food and Drug Administration dated May 29, 1997, approving NDA 20-497. (ATTACHMENT C)

Claim 6: A method of producing an anti-oestrogenic effect in a subject in which such an effect is desired which comprises administering to said subject

an anti-oestrogenic effective amount of a compound as defined in claim 3 or a non-toxic pharmaceutically acceptable salt thereof.

Toremifene citrate is the non-toxic pharmaceutically acceptable citrate salt of the trans-isomer of 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)-ethoxy]phenyl]-1-butene and is the active ingredient in FARESTON®.

Claim 7: A method according to claim 6 in which an antioestrogenic effect is produced in a subject suffering from an oestrogen-dependent tumour.

Toremifene citrate, which is the non-toxic pharmaceutically acceptable citrate salt of the trans-isomer of 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy] phenyl]-1-butene, is the active ingredient in FARESTON®. FARESTON®, as explained above with respect to claims 5 and 6, has been approved for use in the treatment of metastatic breast cancer in postmenopausal women with estrogen receptor positive tumors.

(10) A STATEMENT BEGINNING ON A NEW PAGE, OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A NEW DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG (IND) APPLICATION AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

The Investigational New Drug Application (IND 29,799) for toremifene citrate was filed March 6, 1987 and became effective on March 17, 1987.

The New Drug Application (NDA 20-497) for FARESTON® (toremifene citrate) was submitted on February 3, 1995.

The New Drug Application (NDA 20-497) for FARESTON® (toremifene citrate) was approved by the Food and Drug Administration on May 29, 1997.

Thus, for the purposes of determining the "testing phase" of the "regulatory review period" under 35 U.S.C. §1.56(g)(1)(B)(i), the "testing phase" began on March 17, 1987, the date IND 29,799 became effective and ended on February 3, 1995, the date NDA 20-497 was initially submitted for use of FARESTON® (toremifene citrate) in humans under §505(b) of the Federal Food, Drug, and Cosmetic Act. And, for purposes of determining the "approval phase" of the "regulatory review period" under 35 U.S.C. §1.56(g)(1)(B)(ii) the "approval phase" began on February 3, 1995, the date NDA 20-497 was initially submitted and ended on May 29, 1997, the date on which NDA 20-497 was approved by the FDA.

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

As a brief description of the activities undertaken by Applicant during the applicable regulatory review period, attached hereto is a chronology of the major communications between the Applicant and the FDA from March 6, 1987 to May 29, 1997. (Attachment F)

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR AN EXTENSION AND A STATEMENT AS TO THE LENGTH OF THE EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(i) Applicant is of the opinion that U.S. Patent No. 4,696,949 is eligible for an extension under 35 U.S.C. § 156(a) because it satisfies all of the requirements for such an extension as follows:

35 U.S.C. § 156(a): THE PATENT CLAIMS A PRODUCT, A METHOD OF USING A PRODUCT OR A METHOD OF MANUFACTURING A PRODUCT.

U.S. Patent No. 4,696,949 includes claims covering toremifene citrate, the active ingredient of FARESTON®, a pharmaceutical composition containing toremifene citrate and a method of using toremifene citrate.

35 U.S.C. § 156(a)(1): THE TERM OF THE PATENT HAS NOT EXPIRED BEFORE AN APPLICATION FOR EXTENSION IS SUBMITTED.

U.S. Patent No. 4,696,949 has not expired before submission of this application.

35 U.S.C. § 156(a)(2): THE TERM OF THE PATENT HAS NEVER BEEN EXTENDED UNDER 35 U.S.C. §1.56(e)(1).

The term of U.S. Patent No. 4,696,949 has never been extended under 35 U.S.C. § 156(e)(1).

35 U.S.C. § 156(a)(3): THE APPLICATION FOR EXTENSION IS SUBMITTED BY THE OWNER OF RECORD OF THE PATENT OR ITS AGENT IN ACCORDANCE WITH 35 U.S.C. §1.56(d).

The application for extension is being submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and rules of the United States Patent and Trademark Office.

35 U.S.C. § 156(a)(4): THE PRODUCT HAS BEEN SUBJECT TO A REGULATORY REVIEW PERIOD BEFORE ITS COMMERCIAL MARKETING OR USE; AND

The product FARESTON® has been subjected to a regulatory review period before its commercial marketing or use.

35 U.S.C. § 156(a)(5)(A): THE PERMISSION FOR THE COMMERCIAL MARKETING OR USE OF THE PRODUCT AFTER SUCH REGULATORY REVIEW PERIOD IS THE FIRST PERMITTED COMMERCIAL MARKETING OR USE OF THE PRODUCT USING THE PROVISION OF LAW UNDER WHICH SUCH REGULATORY REVIEW PERIOD OCCURRED.

The commercial marketing or use of the product FARESTON® after the regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug and Cosmetic Act (i.e., Section 505) under which such regulatory review period occurred.

35 U.S.C. § 156(c)(4): ONLY ONE PATENT SHALL BE EXTENDED UNDER 35 U.S.C. §156(e)(1) FOR THE SAME REGULATORY REVIEW PERIOD FOR ANY PRODUCT.

No other patent has been extended for the same regulatory review period for the product FARESTON®.

(ii) The length of the extension of patent term of U.S. Patent No. 4,696,949 claimed by Applicant is 5.00 years, or 1827 days. The length of the extension was determined pursuant to 37 C.F.R. § 1.775(c) and (d) as follows:

1.775(c): The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on March 17, 1987, and ended May 29, 1997, which is a total of 3727 days or 10.21 years, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period", which began on March 17, 1987, and ended on February 3, 1995, which is 7.89 years or 2881 days: and

(2) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Approval Period", which began on February 3, 1995, and ended on May 29, 1997, which is 2.32 years or 846 days.

1.775(d): (1) The regulatory review period, 2188 days, upon which the period of extension is calculated by subtracting from the entire regulatory review period as determined under 37 C.F.R. §1.775(c) (3727 days):

(i) The number of days in the periods of 37 C.F.R. §1.775(c)(1) and (2) which were on or before the date on which the patent issued (September 29, 1987), i.e., 197 days;

(ii) The number of days in the periods of 37 C.F.R. §1.775(c)(1) and (2) during which applicant did not act with due diligence, i.e., zero(0) days; and

(iii) One-half the number of days remaining the period defined by 37 C.F.R. §1.775(c)(1) after the period is reduced in accordance with 37 C.F.R. §1.775(d)(1)(i) and (ii), i.e., (2881 days less 197 days)/2 = 1342 days.

(2) Adding the number of days as determined in 37 C.F.R. §1.775(d)(1) (2188 days or 5.99 years) to the original term of the patent (September 29, 2004) results in the date September 26, 2010;

(3) Adding fourteen (14) years to the date of NDA approval (May 29, 1997) results in the date May 29, 2011;

(4) The earlier of the dates determined in 37 C.F.R. §1.775(d)(2) and (3) is September 26, 2010;

(5) Since U.S. Patent No. 4,696,949 issued after September 24, 1984:

(i) five (5) years added to the original expiration date September 29, 2004 results in the date September 29, 2009; and

(ii) The earlier of the dates determined in 37 C.F.R. §1.775(d)(4) and (5) is September 29, 2009. The length of the patent term is thus 5.00 years.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) THE PRESCRIBED FEES FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION:

The prescribed fee (37 C.F.R. 1.20(j)) for receiving and acting upon this application is attached as a check in the amount of $ 1,090.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 11-1833.

(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THIS APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:

All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

Ronald J. Kubovcik

Kubovcik & Kubovcik

Suite 990, 900 17th Street, N.W.

Washington, DC 20006

Phone: 202-887-9023

Fax: 202-887-9093

(16) A DUPLICATE OF THE APPLICATION PAPERS, CERTIFIED AS SUCH:

Enclosed is a certification that the application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) duplicates thereof (Attachment G).

(17) AN OATH OR DECLARATION SET FORTH IN PARAGRAPH (b) OF THIS SECTION:

The requisite declaration pursuant to 37 C.F.R. § 1.740(b) is attached (Attachment H).

Respectfully submitted,

Ronald J. Kubovcik
Reg. No. 25,401

Dated: July 23, 1997

Attachments:

Power of Attorney (Attachment A)
Product Information Sheet for FARESTON® (Attachment B)
Letter from Food and Drug Administration dated May 29, 1997, Approving NDA 20-497 (Attachment C)
U.S. Patent 4,696,949 (Attachment D)
Copies of Receipts for Maintenance Fees (Attachment E)
Chronology of Regulatory Review Period (Attachment F)
Certification of Copies of Application Papers (Attachment G)
Declaration pursuant to 37 C.F.R. § 1.740(b) (Attachment H)

Power of Attorney
Attachment A

Attorney Docket No. ORI-010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,696,949)
)
Issued: September 29, 1987)
)
To: Reijo J. TOIVOLA; Arto J. KARJALAINEN;)
Kauko O.A. Kurkela; Marja-Liisa SÖDERVALL;)
Lauri V.M. KANGAS; Guillermo L. BLANCO;)
and Hannu K. SUNDQUIST)
)
Assignee: ORION-YHTYMÄ OY)
)
For: NOVEL TRI-PHENYL ALKANE AND ALKENE)
DERIVATIVES AND THEIR PREPARATION)
AND USE)

Assistant Commissioner
for Patents
Washington, D.C. 20231

Sir:

POWER OF ATTORNEY

Assignee, ORION-YHTYMÄ OY, being the owner of the above-identified U.S. Letters Patent, hereby appoints Ronald J. Kubovcik, Reg. No. 25,401, as attorney for ORION-YHTYMÄ OY with regard to an application for extension of the term of U.S. Patent 4,696,949 and to transact all business in the Patent and Trademark Office connected therewith.

U.S. Patent No. 4,696,949
POWER OF ATTORNEY

PATENT

Please send all future correspondence concerning the above matter to Ronald J. Kubovcik at the following address:

Ronald J. Kubovcik
Kubovcik & Kubovcik
900 17th Street, N.W.
Suite 990
Washington, D.C. 20006
Tel: 202-887-9023
Fax: 202-887-9093

Name: Kauko Kurkela
Title: Vice President R&D

ORION-YHTYMÄ OY

Name: Jyrki Mattila
Title: President

Dated: July 11, 1997

Product Information Sheet for FARESTON®
Attachment B

FARESTON® (toremifene citrate) 60 mg Tablets

DESCRIPTION

FARESTON® (toremifene citrate) Tablets for oral administration each contain 88.5 mg of toremifene citrate, which is equivalent to 60 mg toremifene.

Fareston® is a nonsteroidal antiestrogen. The chemical name of toremifene is: 2-[p-[(Z)-4-chloro-1,2-diphenyl-1-butenyl] phenoxy]-N,N-dimethylethylamine citrate (1:1). The structural formula is:

and the molecular formula is: $C_{26}H_{28}ClNO \cdot C_6H_8O_7$. The molecular weight of toremifene citrate is 598.10. The pK_a is 8.0. Water solubility at 37°C is 0.63 mg/ml and in 0.02N HCl at 37°C is 0.38 mg/ml.

FARESTON® is available only as tablets for oral administration. Inactive ingredients: starch, lactose, povidone, sodium starch glycolate, magnesium stearate, microcrystalline cellulose and colloidal silicon dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Toremifene is a nonsteroidal triphenylethylene derivative. Toremifene binds to estrogen receptors and may exert estrogenic, antiestrogenic or both activities,

depending upon the duration of treatment, animal species, gender, target organ or endpoint selected. In general, however, nonsteroidal triphenylethylene derivatives are predominantly antiestrogenic in rats and humans and estrogenic in mice. In rats, toremifene causes regression of established dimethylbenzanthracene (DMBA)-induced mammary tumors. The antitumor effect of toremifene in breast cancer is believed to be mainly due to its antiestrogenic effects, i.e. its ability to compete with estrogen for binding sites in the cancer, blocking the growth-stimulating effects of estrogen in the tumor.

Toremifene causes a decrease in the estradiol-induced vaginal cornification index in some postmenopausal women, indicative of its antiestrogenic activity. Toremifene also has estrogenic activity as shown by decreases in serum gonadotropin concentrations (FSH and LH).

Pharmacokinetics

The plasma concentration of toremifene declines biexponentially after absorption with a mean distribution half-life of about 4 hours and an elimination half-life of about 5 days. Elimination half-lives of major metabolites, N-desmethyltoremifene and 4-hydroxytoremifene were 8 and 4 days, respectively. Mean total clearance of toremifene was approximately 5 L/h.

Absorption and Distribution: Toremifene is well absorbed after oral administration and absorption is not influenced by food. Peak plasma concentrations are obtained within 3 hours. Toremifene displays linear pharmacokinetics after single oral doses of 10 to 680 mg. After multiple dosing, dose proportionality was observed for doses of 10 to 400 mg. Steady state concentrations were reached in about 4–6 weeks. Toremifene has an apparent volume of distribution of 580 L and binds extensively (>99.5%) to serum proteins, mainly to albumin.

Metabolism and Excretion: Toremifene is extensively metabolized, principally by

CYP 450 3A4, to N–desmethyltoremifene, which is also antiestrogenic but with weak *in vivo* antitumor potency. Serum concentrations of N-desmethyltoremifene are 2 to 4 times higher than toremifene at steady state. Toremifene is eliminated as metabolites, predominantly in the feces, with about 10% excreted in the urine during a one week period. Elimination of toremifene is slow, in part because of enterohepatic circulation.

Special populations

Renal Insufficiency: The pharmacokinetics of toremifene and N-desmethyltoremifene were similar in normals and in patients with impaired kidney function.

Hepatic Insufficiency: The mean elimination half-life of toremifene was increased by less than 2-fold in 10 patients with hepatic impairment (cirrhosis or fibrosis) compared to subjects with normal hepatic function. The pharmacokinetics of N-desmethyltoremifene were unchanged in these patients. Ten patients on anticonvulsants (phenobarbital, clonazepam, phenytoin, and carbamazepine) showed a 2-fold increase in clearance and a decrease in the elimination half-life of toremifene.

Geriatric Patients: The pharmacokinetics of toremifene were studied in 10 healthy young males and 10 elderly females following a single 120 mg dose under fasting conditions. Increases in the elimination half-life (4.2 versus 7.2 days) and the volume of distribution (457 versus 627 L) of toremifene were seen in the elderly females without any change in clearance or AUC.

Race: The pharmacokinetics of toremifene in patients of different races has not been studied.

Drug-drug interactions: No formal drug-drug interaction studies with toremifene have been performed.

CLINICAL STUDIES

Three prospective, randomized, controlled clinical studies (North American, Eastern European, and Nordic) were conducted to evaluate the efficacy of FARESTON® in the treatment of breast cancer in postmenopausal women. The patients were randomized to parallel groups receiving FARESTON® 60 mg (FAR60) or tamoxifen 20 mg (TAM20) in the North American Study or tamoxifen 40 mg (TAM40) in the Eastern European and Nordic studies. The North American and Eastern European studies also included high dose toremifene arms of 200 and 240 mg daily, respectively. The studies included postmenopausal patients with tumor estrogen receptor (ER) positive or ER unknown metastatic breast cancer. The patients had at least one measurable or evaluable lesion. The primary efficacy variables were response rate (RR) and time to progression (TTP). Survival (S) was also determined. Ninety-five percent confidence intervals (95% C.I.) were calculated for the difference in RR between the FAR60 and TAM groups and the hazard ratio (relative risk for an unfavorable event, such as disease progression or death, in TAM and FAR60 treated patients) for TTP and S.

Two of the studies showed similar response rates, times to progression, and survival. The Nordic Study showed a trend favoring tamoxifen for these three endpoints, with a statistically significant difference in time to progression.

CLINICAL STUDIES TABLE

Study Treatment Group No. Patients	North American FAR60 TAM20 221 215	East European FAR60 TAM40 157 148	Nordic FAR60 TAM40 214 201
Response CR[1] + PR[2] RR[3] (CR + PR) % Difference in RR 95% C.I.[4] for Difference in RR	14 + 33 11 + 30 21.3 18.1 2.2 -5.8 to 10.2	7 + 25 3 + 28 20.4 20.8 -0.4 -8.5 to 8.8	19 + 48 19 + 56 31.3 37.3 -6.0 -15.1 to 3.1
Time to Progression (TTP) Median TTP (mo.) Hazard Ratio (TAM/FAR) 95% C.I.[4] for Hazard Ratio (%)	5.8 5.8 1.01 0.81 to 1.28	4.8 5.0 1.02 0.79 to 1.31	7.3 10.2 0.80 0.64 to 1.00
Survival (S) Median S (mo.) Hazard Ratio (TAM/FAR) 95% C.I.[4] for Hazard Ratio (%)	33.6 34.0 0.96 0.74 to 1.24	25.4 23.4 0.88 0.72 to 1.28	33.0 38.7 0.84 0.73 to 1.22

[1]CR = complete response; [2]PR = partial response; [3]RR = response rate; [4]C.I. = confidence interval

The high dose groups, toremifene 200 mg daily in the North American Study and 240 mg daily in the Eastern European Study, were not superior to the lower toremifene dose groups, with response rates of 22.6% and 28.7%, median times to progression of 5.6 and 6.1 months, and median survivals of 30.1 and 23.8 months, respectively.

The median treatment duration in the three pivotal studies was 5 months (range 4.2 - 6.3 months).

INDICATION AND USAGE

FARESTON® is indicated for the treatment of metastatic breast cancer in postmenopausal women with estrogen receptor positive or receptor unknown tumors.

CONTRAINDICATIONS

FARESTON® is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hypercalcemia and Tumor Flare: As with other antiestrogens, hypercalcemia and tumor flare have been reported in some breast cancer patients with bone metastases during the first weeks of treatment with FARESTON®. Tumor flare is a syndrome of diffuse musculoskeletal pain and erythema with increased size of tumor lesions that later regress. It is often accompanied by hypercalcemia. Tumor flare does not imply failure of treatment or represent tumor progression. If hypercalcemia occurs, appropriate measures should be instituted; if hypercalcemia is severe FARESTON® treatment should be discontinued.

Tumorigenicity: Since most toremifene trials have been conducted in patients with metastatic disease, adequate data on the potential endometrial tumorigenicity of long-term treatment with FARESTON® are not available. Endometrial hyperplasia has been reported. Patients treated with Fareston® have developed endometrial cancer, but the circumstances (short duration of treatment and prior treatment and pre-malignant conditions) make it impossible to establish the role of Fareston®.

Endometrial hyperplasia of the uterus was observed in monkeys following 52 weeks of treatment at ≥ 1mg/kg and in dogs following 16 weeks of treatment at ≥ 3mg/kg with toremifene (about 1/4 and 1.4 times, respectively, the daily maximum recommended human dose on a mg/m^2 basis).

Pregnancy

FARESTON® may cause fetal harm when administered to pregnant women. Studies in rats at doses equal to or greater than 1.0 mg/kg/day (about 1/4 the daily maximum recommended human dose on a mg/m^2 basis) administered during the period of organogenesis, have shown that toremifene is embryotoxic and fetotoxic.

as indicated by intrauterine mortality, increased resorption, reduced fetal weight, and fetal anomalies including malformation of limbs, incomplete ossification, misshapen bones, rib/spine anomalies, hydroureter, hydronephrosis, testicular displacement and subcutaneous edema. Fetal anomalies may have been a consequence of maternal toxicity. Toremifene has been shown to cross the placenta and accumulate in the rodent fetus.

In rodent models of fetal reproductive tract development, toremifene produced inhibition of uterine development in female pups similar to diethylstilbestrol (DES) and tamoxifen. The clinical relevance of these changes is not known. Neonatal rodent studies have not been conducted to assess the potential for toremifene to cause other DES-like effects in offspring (i.e., vaginal adenosis). Vaginal adenosis has been observed following treatment with other drugs of this class.

Embryotoxicity and fetotoxicity were observed in rabbits at doses equal to or greater than 1.25 mg/kg/day and 2.5 mg/kg/day, respectively (about 1/3 and 2/3 the daily maximum recommended human dose on a mg/m^2 basis); fetal anomalies included incomplete ossification and anencephaly.

There are no studies in pregnant women. If FARESTON® is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

PRECAUTIONS

General: Patients with a history of thromboembolic diseases should generally not be treated with FARESTON®. In general, patients with pre-existing endometrial hyperplasia should not be given long-term FARESTON® treatment. Patients with bone metastases should be monitored closely for hypercalcemia during the first weeks of treatment (See: WARNINGS). Leukopenia and thrombocytopenia have

been reported rarely; leukocyte and platelet counts should be monitored when using Fareston® in patients with leukopenia or thrombocytopenia.

Information for patients

Vaginal bleeding has been reported in patients using FARESTON®. Patients should be informed about this and instructed to contact their physician if such bleeding occurs.

Patients with bone metastases should be informed about the typical signs and symptoms of hypercalcemia and instructed to contact their physician for further assessment if such signs or symptoms occur.

Laboratory tests

Periodic complete blood counts, calcium levels and liver function tests should be obtained.

Drug–drug interactions

Drugs that decrease renal calcium excretion, e.g., thiazide diuretics, may increase the risk of hypercalcemia in patients receiving FARESTON®. There is a known interaction between antiestrogenic compounds of the triphenylethylene derivative class and coumarin–type anticoagulants (e.g. warfarin), leading to an increased prothrombin time. When concomitant use of anticoagulants with FARESTON® is necessary, careful monitoring of the prothrombin time is recommended.

Cytochrome P450 3A4 enzyme inducers, such as phenobarbital, phenytoin and carbamazepine, increase the rate of toremifene metabolism, lowering the steady state concentration in serum. Metabolism of toremifene may be inhibited by drugs known to inhibit the CYP 3A4–8 enzymes. Examples of such drugs are ketoconazole and similar antimycotics as well as erythromycin and similar macrolides. This interaction has not be studied and its clinical relevance is

uncertain.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
Conventional carcinogenesis studies in rats at doses of 0.12 to 12 mg/kg/day (about 1/100 to 1.5 times the daily maximum recommended human dose on a mg/m^2 basis) for up to 2 years did not show evidence of carcinogenicity. Studies in mice at doses of 1.0 to 30.0 mg/kg/day (about 1/15 to 2 times the daily maximum recommended human dose on a mg/m^2 basis) for up to 2 years revealed increased incidence of ovarian and testicular tumors, and increased incidence of osteoma and osteosarcoma. The significance of the mouse findings is uncertain because of the different role of estrogens in mice and the estrogenic effect of toremifene in mice. Estrogen stimulates murine bone deposition but inhibits bone formation and resorption in humans. An increased incidence of ovarian and testicular tumors in mice has also been observed with other human antiestrogenic agents that have primarily estrogenic activity in mice.

Toremifene has not been shown to be mutagenic in *in vitro* tests (Ames and E. coli bacterial tests) or clastogenic either *in vitro* (chromosomal aberrations in CHL/IU cells or human lymphocytes) or *in vivo* (micronucleus test in mice). No significant adduct formation could be detected using ^{32}P post-labeling in liver DNA from rats administered toremifene when compared to tamoxifen at similar doses. A study in cultured human lymphocytes indicated that adducting activity of toremifene, detected by ^{32}P post-labeling, was about 1/6 that of tamoxifen at approximately equipotent concentrations. In addition, the DNA adducting activity of toremifene in salmon sperm, using ^{32}P post-labeling, was 1/6 and 1/4 that observed with tamoxifen at equivalent concentrations following activation by rat and human microsomal systems, respectively. However, toremifene exposure is 4-fold the exposure of tamoxifen based on human AUC in serum at recommended clinical doses.

Toremifene produced impairment of fertility and conception in male and female rats at doses equal to or greater than 25.0 and 0.14 mg/kg/day, respectively (about 3.5 times and 1/50 the daily maximum recommended human dose on a mg/m^2 basis). At these doses, sperm counts, fertility index and conception rate were reduced in males with atrophy of seminal vesicles and prostate. In females, fertility and reproductive indices were markedly reduced with increased pre- and post-implantation loss. In addition, offspring of treated rats exhibited depressed reproductive indices. Toremifene produced ovarian atrophy in dogs administered doses equal to or greater than 3 mg/kg/day (about 1.5 times the daily maximum recommended human dose on a mg/m^2 basis) for 16 weeks. Cystic ovaries and reduction in endometrial stromal cellularity were observed in monkeys at doses equal to or greater than 1 mg/kg/day (about 1/4 the daily maximum recommended human dose on a mg/m^2 basis) for 52 weeks.

Pregnancy: Pregnancy Category D (See: WARNINGS).

Nursing Mothers: Toremifene has been shown to be excreted in the milk of lactating rats. It is not known if this drug is excreted in human milk. (See: WARNINGS and PRECAUTIONS).

Pediatric Use: There is no indication for use of FARESTON® in pediatric patients.

Geriatric Use: The median ages in the three controlled studies ranged from 60 to 66 years. No significant age-related differences in FARESTON® effectiveness or safety were noted.

Race: Fourteen percent of patients in the North American study were non-caucasian. No significant race-related differences in FARESTON® effectiveness or safety were noted.

ADVERSE REACTIONS

Adverse drug reactions are principally due to the anti-estrogenic hormonal actions of FARESTON® and typically occur at the beginning of treatment.

The incidences of the following eight clinical toxicities were prospectively assessed in the North American Study. The incidence reflects the toxicities that were considered by the investigator to be drug-related or possibly drug-related.

	North American Study	
	FAR 60	TAM 20
	n = 221	n = 215
Hot flashes	35%	30%
Sweating	20%	17%
Nausea	14	15%
Vaginal Discharge	13%	16%
Dizziness	9%	7%
Edema	5%	5%
Vomiting	4%	2%
Vaginal bleeding	2%	4%

Approximately 1% of patients receiving FARESTON® (n = 592) in the three controlled studies discontinued treatment as a result of adverse events (nausea and vomiting, fatigue, thrombophlebitis, depression, lethargy, anorexia, ischemic attack, arthritis, pulmonary embolism and myocardial infarction).

Serious adverse events occurring in at least 1% of patients in the three major trials are listed in the table below.

Adverse Event	North American		East European		Nordic	
	FAR60 N=221(%)	TAM20 N=215(%)	FAR60 N=157(%)	TAM40 N=149(%)	FAR60 N=214(%)	TAM40 N=201(%)
Cardiac						
Cardiac Failure	2(1)	1(<1)	——	1(<1)	2(1)	3(1.5)
Myocardial Infarction	2(1)	3(1.5)	1(<1)	2(1)	——	1(<1)
Arrhythmia	——	——	——	——	3(1.5)	1(<1)
Angina Pectoris	——	——	1(<1)	——	1(<1)	2(1)
Ocular*						
Cataracts	22(10)	16(7.5)	——	——	——	5(3)
Dry Eyes	20(9)	16(7.5)	——	——	——	——
Abnormal Visual Fields	8(4)	10(5)	——	——	——	1(<1)
Corneal Keratopathy	4(2)	2(1)	——	——	——	——
Glaucoma	3(1.5)	2(1)	1(<1)	——	——	1(<1)
Abnormal Vision/Diplopia	——	——	——	——	3(1.5)	——
Thromboembolic						
Pulmonary Embolism	4(2)	2(1)	1(<1)	——	——	1(<1)
Thrombophlebitis	——	2(1)	1(<1)	1(<1)	4(2)	3(1.5)
Thrombosis	——	1(<1)	1(<1)	——	3(1.5)	4(2)
CVA/TIA	1(<1)	——	——	1(<1)	4(2)	4(2)
Elevated Liver Tests						
SGOT	11(5)	4(2)	30(19)	22(15)	32(15)	35(17)
Alkaline Phosphatase	41(19)	24(11)	16(10)	19(8)	18(8)	31(15)
Bilirubin	3(1)	4(2)	2(1)	1(<1)	2(1)	6 3(1.5)(3)
Hypercalcemia	6(3)	6(3)	1(<1)	——	——	——

*Most of the ocular abnormalities were observed in the North American Study in which on-study and biannual ophthalmic examinations were performed. No cases of retinopathy were observed in any arm.

endo cancer

Other adverse events of unclear causal relationship to FARESTON® included leukopenia and thrombocytopenia, skin discoloration or dermatitis, constipation, dyspnea, paresis, tremor, vertigo, pruritus, anorexia, reversible corneal opacity (corneal verticulata), asthenia, alopecia, depression, jaundice and rigors.

The incidence of SGOT elevations was statistically significantly greater in the 200 and 240 mg FARESTON® dose arms than in the tamoxifen arms. Higher doses of FARESTON® were also associated with a statistically significant increase in nausea. Approximately 4% of patients were withdrawn for toxicity from the high dose FARESTON® treatment arms. Reasons for withdrawal included, hypercalcemia, abnormal liver function tests and one case each of toxic hepatitis, depression, dizziness, incoordination, ataxia, blurry vision, diffuse dermatitis and a constellation of symptoms consisting of nausea, sweating and tremor.

OVERDOSAGE

Lethality was observed in rats following single oral doses that were equal to or greater than 1000 mg/kg (about 150 times the recommended human dose on a mg/m^2 basis) and was associated with gastric atony/dilatation leading to interference with digestion and adrenal enlargement.

Vertigo, headache and dizziness were observed in healthy volunteer studies at a daily dose of 880 mg for five days. The symptoms occurred in two of the five subjects during the third day of the treatment and disappeared within two days of discontinuation of the drug. No immediate concomitant changes in any measured clinical chemistry parameters were found. In a study in postmenopausal breast cancer patients, toremifene 400 mg/m^2/day caused dose-limiting nausea, vomiting and dizziness, as well as reversible hallucinations and ataxia in one patient.

Theoretically, overdose may be manifested as an increase of anti-estrogenic effects, such as hot flashes, estrogenic effects, such as vaginal bleeding, or nervous system disorders, such as vertigo, dizziness, ataxia and nausea. There is no specific antidote and the treatment is symptomatic.

DOSAGE AND ADMINISTRATION

The dosage of FARESTON® is 60 mg, once daily, orally. Treatment is generally continued until disease progression is observed.

HOW SUPPLIED

FARESTON® Tablets, containing toremifene citrate in an amount equivalent to 60 mg of toremifene, are round, convex, unscored, uncoated, and white or almost white. FARESTON® Tablets are identified with TO 60 embossed on one side.

FARESTON® Tablets are available as:

NDC-0085-1126-01 bottles of 30

NDC 0085-1126-02 bottles of 100

NDC 0085-1126-XX box of 5 envelopes, each with a blister pack of 7 tablets (total of 35 tablets), patient starter packages.

Store at 25°C (77°F). Protect from heat and light.

Schering Corporation
Kenilworth, NJ 07033 USA

Letter from Food and Drug Administration dated May 29, 1997, Approving NDA 20-497 Attachment C

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

NDA 20-497

Food and Drug Administration
Rockville MD 20857

MAY 29 1997

Orion Corporation, Orion Farmos
433 Airport Blvd., Suite 327
Burlingame, CA 94010-2010

Attention: Daniel L. Azarnoff, M.D.
President, D.L. Azarnoff Associates

Dear Dr. Azarnoff:

Please refer to your new drug application dated December 19, 1994, received December 20, 1994, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fareston (toremifene citrate) 60 mg Tablets.

We acknowledge receipt of your submissions dated January 15 and 22, February 5, March 3, and April 7, 1997. The original user fee goal date for this application was January 3, 1996. Your submission of May 2, 1996 in response to our approvable letter of January 3, 1996 extended the user fee goal date to November 1, 1996. The submission of January 22, 1997 in response to our approvable letter of October 31, 1996 extended the user fee goal date to July 24, 1997.

This new drug application provides for the treatment of metastatic breast cancer in postmenopausal women with estrogen receptor positive or receptor unknown tumors.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this

submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-497. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We note that your April 29, 1997 submission of promotional materials is under review and that the patient brochure will need revision in order to confrom to the revised labeling.

A neonatal rodent study (including a positive DES control) will need to be conducted prior to expanding the current indication for toremifene. This will be used to assess the potential for toremifene to cause other DES-like effects in offspring (i.e., vaginal adenosis). The NCTR study which observed the inhibition of uterine gland genesis in female rodents following treatment with toremifene is not sufficient to assess the complete reproductive tract toxicity. Results from this study may also be used to revise the labeling with the current indication.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Linda McCollum, Project Manager, at (301) 594-5771.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

U.S. Patent No. 4,696,949
Attachment D

United States Patent [19]

Toivola et al.

[11] **Patent Number: 4,696,949**

[45] **Date of Patent: Sep. 29, 1987**

[54] **NOVEL TRI-PHENYL ALKANE AND ALKENE DERIVATIVES AND THEIR PREPARATION AND USE**

[75] Inventors: **Reijo J. Toivola; Arto J. Karjalainen,** both of Oulu; **Kauko O. A. Kurkela,** Oulu; **Marja-Liisa Soderwall,** Oulu; **Lauri V. M. Kangas,** Turki; **Guillermo L. Blanco,** Oulu; **Hannu K. Sunduiqst,** Kaarina, all of Finland

[73] Assignee: **Farmos Group Ltd.,** Turku, Finland

[21] Appl. No.: **823,856**

[22] Filed: **Jan. 29, 1986**

Related U.S. Application Data

[63] Continuation of Ser. No. 497,813, May 25, 1983, abandoned.

[30] **Foreign Application Priority Data**

Jun. 25, 1982 [GB] United Kingdom 8218414

[51] **Int. Cl.**[4] **A61K 31/135;** C07C 91/06

[52] **U.S. Cl.** **514/648;** 564/324; 564/299; 514/644

[58] **Field of Search** 564/324, 299; 514/644

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

1015787 1/1966 United Kingdom .

OTHER PUBLICATIONS

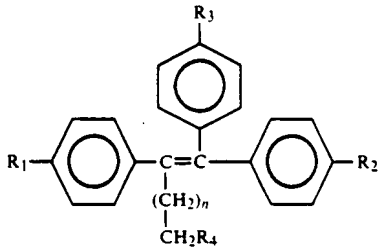
Catlaneo et al., Farmaco 15 1960; pp. 632-641.
Xn et al., Acta Pharmaceutica Sinica 15 (11) 1980, pp. 648-655
Curtin et al., J. Amer. Chem. Soc. 77, 1955, pp. 4566-4570.
Koelach, J.A.C.S. 54 1932; pp. 2045-2048.
Hassner et al., J. Org. Chem. 36 (15) 1971; pp. 2176-2180.
Hassner et al., J. Org. Chem. 35 (10) 1970; pp. 3397-3401.
Normen et al., J. Chem. Soc. B 1967 (6), pp. 598-604.
Simamura et al., Bull. Chem. Soc. Japan 27 1954; pp. 231-235.
Polman et al., Recl. Trav. Chim. Pays. Bas 92, 1973; pp. 845-854.
Bergnener et al., Ber. 66B; 1933; pp. 54-58.
Bonner, J. Amer. Chem. Soc. 81, 1954; pp. 1181-1183.
Norman et al., J. Chem. Soc. B. 1967 (6), pp. 604-611.
Dormon et al., Ber. Jahrg, 87. 5 1954, p. 630.
Yaulx et al., J. Org. Chem. 30 (1) 1965, pp. 58-60.
Muihailovic et al., Tetrahedron 1978, 34(16), pp. 2587-2589.

(List continued on next page.)

Primary Examiner—Nicky Chan
Attorney, Agent, or Firm—Armstrong, Nikaido, Marmelstein & Kubovcik

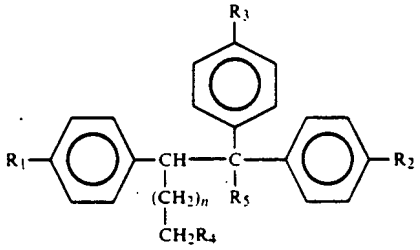
[57] **ABSTRACT**

The invention provides novel compounds of the formula:



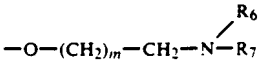
(I)

and



(II)

wherein n is 0 to 4, R_1 and R_2, which can be the same or different are H, OH, alkoxy of 1 to 4 carbon atoms, benzyloxy or methoxymethoxy; R_3 is H, OH, halogen, alkoxy of 1 to 4 carbon atoms, benzyloxy, methoxymethoxy, 2,3-dihydroxypropoxy or



wherein m is 1 or 2, R_6 and R_7, which can be the same or different are H or an alkyl group of 1 to 4 carbon atoms, or

can form an N-containing three-, four-, five- or six-membered heterocyclic ring; R_4 is OH, F, Cl, Br, I, mesyloxy, tosyloxy, alkylcarbonyloxy of 1 to 4 C-atoms, formyloxy or CH_2R_4 is replaced by CHO; R_5 is H or OH; or R_4 and R_5 together form an —O— bridge between the carbon atoms to which they are attached, and their non-toxic pharmaceutically acceptable salts and esters and mixtures thereof. Processes for the preparation of these compounds are described, and also novel pharmaceutical compositions containing them. These compounds exhibit valuable pharmacological properties as estrogenic, anti-estrogenic, and progestanic agents. They are also effective against oestrogen-dependent tumors. Certain compounds are useful as chemical intermediates for the preparation of pharmacologically active compounds of the invention.

7 Claims, No Drawings

Copies of Receipts of Maintenance Fees
Attachment E

Computer Patent Annuities
PATENT, DESIGN & TRADE MARK RENEWALS WORLD WIDE
TRADE MARK SEARCHING

R.S. CHINNERY, B.Sc. CPA
R.C. WALKER, MA, CPA
G.S. COLLINS, CPA

J. ONSLOW
SUE McI FAN, BA
M.B.W TFIELD, B.Sc.
C.A. HL N, B.Sc. Dip Eng. ACA

Telephone: 0534 75101
Fax: 0534 XXXX 66460
Telex: 4192137 COPAN G
Cable: COPAN,JERSEY

PO Box 778 Jersey JE1 1BL Channel Islands

OFFICIAL RECEIPT/RENEWAL CERTIFICATE

ORION CORP.FARMOS
INTERNATIONAL PROPERTY DEPT.
P.O.B.425
SF-20101 TURKU 10
FINLAND

7046

We enclose the official receipt for the following patent. This document should be kept in a safe place in case proof of renewal is required at any time. If you would like your official receipts kept and stored here in future, please let us know by signing and returning this letter: a fee of £1 for this service would then be added to each future invoice for annuities paid on your account.

Date 05 JUL 91

1788 Account 64922

Country	Patent No.	Due Date	Annuity	Your Reference Patentee
USA (FULL FEES)	4696949-US	MAR.29	04	FC-1000 FARMOS GROUP LTD-823856-29JAN86

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000197

75M3/0406

COMPUTER PATENT ANNUITIES
C/O COMPUTER PATENT ANNUITITES, INC.
1111 JEFFERSON DAVIS HIGHWAY
SUITE 514, CRYSTAL GATEWAY NORTH
ARLINGTON, VA 22202

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,696,949	184	1930	----	06/823,856	09/29/87	01/29/86	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	P418-566-K83

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

Chronology of Regulatory Review Period
Attachment F

Chronology of Events on FARESTON® (toremifene citrate)
IND 29,799
NDA 20-497

March 6, 1987	IND for FARESTON® submitted to FDA.
March 17, 1987	A. Sindelar (assigned CSO) called L. Irminger (Adria DRA). Questions concerning clinical monitor CV were answered.
March 17, 1987	Acknowledgement of receipt of IND; IND Number 29,799 assigned for FARESTON®.
April 6, 1987	Dr. S. Stolzenberg called L. Irminger to request additional information concerning toxicology report (tamoxifen).
April 9, 1987	L. Irminger called Dr. S. Stolzenberg to tell that Farmos has to be contacted for toxicology information previously requested.
April 10, 1987	A. Sindelar called L. Irminger to inform that Phase I study may proceed. Several points discussed concerning clinical, pharmacology/ toxicology, and manufacturing and controls sections of IND. A letter regarding CMC section will follow.
April 10, 1987	Amendment to protocol submitted (CS092003).
May 29, 1987	Response to clinical and pharmacology/ toxicology issues of April 10, 1987 communication submitted to FDA. Farmos waiting for the letter concerning CMC questions.
June 16, 1987	FDA completed the review of the IND.

June 16, 1987	Letter from FDA informing that clinical studies may proceed and requesting information and giving recommendations regarding clinical and chemistry sections of the application.
June 29, 1987	Teleconference between D. Harry, L. Irminger and Dr. R. Justice regarding statistical considerations for April 10, 1987 amendment. The need to notify investigators and IRBs that tamoxifene had been reported to be carcinogenic in animals was discussed.
July 8, 1987	R. Justice called L. Irminger to ask Adria to notify investigators that tamoxifene is reported to be carcinogenic in animals.
July 15, 1987	L. Irminger called S. Stolzenberg to provide information on the toxicology report requested April 6, 1987.
July 15, 1987	A letter was sent to FDA confirming July 15, 1987 telephone communication.
July 22, 1987	L. Irminger called A. Sindelar. Oncology division classified toremifene I-C.
July 29, 1987	Letter from R. Gams, M.D., to D. Buell, M.D. (FDA) requesting for compassionate use.
August 11, 1987	A. Sindelar called L. Irminger to inform that L. Versteegh who was in Washington D.C. for a meeting should be provided with Farmos DMF letter from FDA.
August 17, 1987	Amendment concerning Manufacturing and Controls sections submitted.
August 17, 1987	Amendment providing FDA bulk finished product for repackaging and labelling for clinical trials.

August 17, 1987	Response to FDA concerning clinical and chemistry issues of June 16, 1987 letter.
September 8,1987	Compassionate Use Request submitted. Documents for the July 29, 1987 request submitted.
September 18, 1987	IND Safety Report submitted (CS092002, ARR09287001).
September 30, 1987	IND Safety Report submitted (CS092002, ARR09287002).
October 30, 1987	IND Safety Report submitted (CS092002, ARR09287003).
November 18, 1987	L. Versteegh called A. Sindelar . Dr. Justice identified as medical officer. Compassionate use request discussed.
November 18, 1987	Compassionate Use Request submitted.
December 9, 1987	IND Safety Report submitted (follow up of CS092002, ARR09287003).
December 17, 1987	IND Safety Report submitted (CS092002, ARR09287004).
December 23, 1987	IND Safety Report submitted (CS092002, ARR09287005).
January 11, 1988	D. Jones called R. Justice regarding the compassionate use request.
January 26, 1988	IND Safety Report submitted (CS092002, ARR09288001).

February 3, 1988	Compassionate Use Request submitted.
February 11, 1988	DMF 6652 updated to include new options for sourcing of raw materials.
March 14, 1988	D. Jones called A. Sindelar. End-of-Phase II meeting was discussed.
March 25, 1988	D. Jones called A. Sindelar giving more details regarding End-of-Phase II meeting.
April 6, 1988	D.Jones called A.Sindelar regarding the compassionate use request.
April 13, 1988	IND Safety Report submitted (preclinical).
April 15, 1988	Correction to Safety Report of January 28, 1988 (CS092002, ARR09288001) submitted.
April 18, 1988	Compassionate Use Request submitted.
April 18, 1988	IND Safety Report submitted (CS092002, ARR09288005).
April 18, 1988	Amendment to protocol CS092003 submitted.
May 4, 1988	D. Jones called A. Sindelar regarding the compassionate use request.
May 19, 1988	Compassionate Use Request submitted.
May 26, 1988	Amendment concerning Pharmacology/ Toxicology and Clinical sections submitted.

June 3, 1988	D. Jones called A. Sindelar regarding the compassionate use request.
June 8, 1988	IND Safety Report submitted (CS092002, ARR09288006).
June 14, 1988	Amendment concerning Clinical and Preclinical sections submitted. Request for End-of-Phase II meeting.
June 15, 1988	Annual Progress Report submitted.
June 15, 1988	Compassionate Use Request submitted.
June 20, 1988	A. Sindelar called D. Jones giving comments from Dr. Justice on informed consent form of the compassionate use request of June 15, 1988.
June 22, 1988	A. Sindelar called D. Jones. End-of-Phase II meeting scheduled.
July 8, 1988	Amendment to ptotocol CS092003 submitted.
July 19, 1988	Letter to FDA providing a list of attendees for August 9, 1988 End-of-Phase II meeting.
July 21, 1988	IND Safety Report submitted (ARR09288007, foreign).
August 1, 1988	A follow-up to April 13, 1988 preclinical studies report submitted.
August 9, 1988	End-of-Phase II meeting at FDA.
August 19, 1988	Compassionate Use Request submitted.
August 19, 1988	IND Safety Report submitted (CS092002, ARR09288008).

August 30, 1988	IND Safety Report submitted (CS092002, ARR09288009).
September 1, 1988	Compassionate Use Request submitted.
September 2, 1988	Amendment submitted. New Protocol CS092011.
September 2, 1988	Amendment submitted. New Protocol CS092006.
October 13, 1988	IND Safety Report submitted (ARR09288010, foreign).
October 19, 1988	IND Safety Report submitted (CS092002, ARR09288011).
November 4, 1988	Letter to FDA confirming the November 10, 1988 meeting to discuss proposed carcinogenicity studies.
November 10, 1988	FDA meeting. Discussion of carcinogenicity studies.
November 10, 1988	FDA minutes of the meeting.
November 15, 1988	Cathy Schumaker (CSO) called D. Jones. Submitting CVs of ophthalmologists discussed.
November 22, 1988	Letter from Adria (Douglas R Jones) to FDA (John Palmer, Dir Division of Oncology/Radio pharmaceutical Drug Products) submitting the minutes of November 10, 1988 meeting.
November 22, 1988	Dose finding studies submitted.
December 14, 1988	Amendment concerning Clinical, CMC and Preclinical sections submitted.
December 19, 1988	IND Safety Report submitted (CS092002, ARR09288012).

December 22, 1988	Letter from FDA. May proceed with protocol CS092011. Questions and comments about the statistical considerations.
December 22, 1988	FDA minutes of the August 9, 1988 and November 10, 1988 meetings.
January 20, 1989	D. Jones called C. Schumaker. Comments on December 22, 1988 letter regarding objectives of study discussed.
February 3, 1989	Teleconference between Gams/Jones/Shemano and R. Justice regarding proposed protocol amendment concerning bone lesions.
February 7, 1989	Amendment submitted (New Protocol CS092010).
February 24, 1989	Response to the December 22, 1988 letter from FDA submitted.
March 8, 1989	D. Jones called Dr. David Richman, Supervisory Pharmacologist, regarding a second l-year chronic toxicity study in non-rodent species.
March 20, 1989	Amendment concerning Clinical and Pharmacology sections submitted.
March 29, 1989	Amendments to protocols CS092006 and CS092011 submitted.
April 11, 1989	IND Safety Report submitted (CS092011, ARR09289002).
April 17, 1989	IND Safety Report submitted (CS092011, ARR09289001).
April 19, 1989	Letter to FDA informing that two safety reports represent same events (ARR09288008 and ARR09288012).

April 28, 1989	Letter to FDA submitting additional investigator CVs.
April 28, 1989	IND Safety Report submitted (Foreign ARR09289003 and ARR09289004)
May 24, 1989	IND Safety Reports submitted (CS092002, ARR09288013 and ARR09289006; CS092010, ARR09289007; CS092011, ARR09289005).
May 24, 1989	Annual Progress Report submitted.
June 1, 1989	IND Safety Report submitted (Foreign ARR09289008 and ARR09289009).
July 6, 1989	IND Safety Report submitted (CS092006, ARR09289010).
July 11, 1989	Amendment submitted (New Protocol CS092016).
July 18, 1989	Amendment concerning Clinical and Preclinical sections submitted.
July 19, 1989	D. Jones called C. Schumaker regarding a patient moving to another state. Associate investigator is to be added to facilitate continued treatment.
July 25, 1989	IND Safety Report submitted (ARR09289011, foreign).
August 2, 1989	IND Safety Report submitted (CS092010, ARR09289012).
August 7, 1989	IND Safety Report submitted (CS092006, ARR09289013; CS092010,ARR09289014).
August 17, 1989	Dr.Edward Bashaw, of Biopharmaceutics, called D.Jones regarding the status of CS092016.

August 28, 1989	Amendment containing updated stability data submitted.
August 29, 1989	Correction to Safety Report CS092002, ARR09289005 submitted.
August 29, 1989	IND Safety Reports submitted (CS092006, ARR09289015; CS092011,ARR09289016; CS092010,ARR09289017).
September 14, 1989	Amendment concerning Pharmacology/Toxicology sections submitted.
September 18, 1989	IND Safety Report submitted (CS092010, ARR09289018).
September 22, 1989	D. Jones called C. Schumaker regarding the compassionate use request.
September 26,1989	IND Safety Report submitted (CS092011, ARR09289020).
September 27, 1989	Compassionate Use Request submitted.
September 28, 1989	Amendment concerning Manufacturing and Controls sections submitted.
October 2, 1989	IND Safety Report submitted (CS092010, ARR09289021).
October 11, 1989	IND Safety Report submitted (CS092010, ARR09289019).
October 12, 1989	Amendments to protocols CS092006, CS092010, and CS092011 submitted.
October 16, 1989	Correction to Safety Reports ARR09289013 and ARR09289015 submitted.
October 18, 1989	IND Safety Report submitted (ARR09289022, foreign).

October 18, 1989	IND Safety Report submitted (CS092011, ARR09289023).
October 18, 1989	Teleconference between D. Jones, Dr. L. Wong and Dr. Will Coulter (Acting Supervisory Pharmacologist). Dr. Coulter was spoken to in Dr. Richman's absence. Feasibility/need for SEG III rat study discussed.
October 18, 1989	Letter from FDA giving comments on February 24, 1989 response to December 22, 1988 letter regarding Phase III protocol.
October 23, 1989	D. Jones called C. Schumaker regarding Dr. Williams questions why deaths due to progressive disease are submitted as prompt reports. Consideration for a compassionate use protocol in endometrial cancer discussed.
October 27, 1989	IND Safety Report submitted (ARR09289024, foreign).
October 31, 1989	Amendment submitted. Addition of non-U.S. investigators. Canadian CS092006 protocol submitted.
November 1, 1989	D. Jones called W. Coulter. FDA will not require a SEG III study to support an adjuvant indication for toremifene.
November 8, 1989	A follow-up to ARR09289009, foreign, submitted.
November 9, 1989	Letter to FDA requesting for a meeting to discuss the following proposals: collapsing two ongoing Phase III U.S. studies due to diminishing source of eligible patients and use of Farmos Scandinavian and Soviet studies as additional adequate and well controlled study.
December 14, 1989	Letter to FDA submitting comments requested on International Breast Cancer Study Group (IBCSG) protocol studying toremifene in an adjuvant setting.

December 14, 1989	IND Safety Report submitted (CS092010, ARR09289025).
December 14, 1989	D. Jones called C. Schumaker regarding a question on batch size for stability studies for Dr. Hoiberg, Supervisory Chemist. The answer was not specific. Reference made to guidelines.
December 20, 1989	Amendment concerning Manufacturing and Controls sections submitted.
December 20, 1989	C. Schumaker called D. Jones regarding meeting to discuss options for dealing with diminishing source of patients scheduled for February 7, 1990.
January 3, 1990	IND Safety Report submitted (CS092010, ARR09289026).
January 4, 1990	C. Schumaker called D. Jones confirming meeting for February 7, 1990. Meeting topics discussed.
January 10, 1990	D. Jones called C. Schumaker regarding comments on IBCSG adjuvant protocol needed by last week of February.
January 13, 1990	Protocol amendment submitted.
January 19, 1990	Letter to FDA submitting a second draft of IBCSG protocol for comments.
January 25, 1990	D. Jones called C. Schumaker reminding about the request for comments on IBCSG protocol.
January 31, 1990	Letter to FDA submitting a list of attendees for February 7, 1990 meeting and a response to comments in October 18, 1989 letter.

February 7, 1990	Meeting with FDA. Two U.S. Phase III studies to be collapsed into one multicenter study, to remain a three arm study and incorporate an interim analysis. Additional non-U.S. Phase III studies will be included as supportive studies.
February 8, 1990	Dr. Hoberman called R. Gams to discuss again two issues of the February 7, 1990 meeting.
February 14, 1990	IND Safety Report submitted (CS092006, ARR09290001; Follow-up ARR09289024, foreign).
February 15, 1990	Letter to FDA submitting minutes of the February 7, 1990 meeting.
February 15, 1990	IND Safety Report submitted (CS0920ll, ARR09290002).
February 26, 1990	Fax from FDA (R. Justice/J. Johnson) submitting comments on IBCSG adjuvant protocol.
February 27, 1990	IND Safety Report submitted (CS092006, ARR09290003).
March 6, 1990	IND Safety Report submitted (CS092006, ARR09290004).
March 8, 1990	IND Safety Report submitted (Follow-up CS092006, ARR09290003).
March 12, 1990	Letter to FDA confirming FDA the position that Segment I and III studies not required for a cancer indication nor for an adjuvant claim for toremifene.
March 13, 1990	Amendment concerning Clinical and Preclinical sections submitted.

March 19, 1990	IND Safety Reports submitted (Foreign ARR09290005, ARR09290006, ARR09290007; follow-up CS092011, ARR09289020).
March 21, 1990	D. Brott called C. Schumaker concerning information regarding Nordic and Soviet trial which was requested in the February 7, 1990 meeting to be sent.
March 26, 1990	Letter to FDA regarding differences between U.S. standards and those practiced in the Nordic countries and the Soviet Union regarding IRBs and informed consent. A draft of amended protocols for the Nordic and Soviet studies included.
March 26, 1990	Brott and Shemano called C. Schumaker regarding a compassionate use request for desmoid tumor. Is to be discussed with Dr. Justice.
March 27, 1990	C. Schumaker called Brott and Shemano to discuss further the compassionate use request. A permission to treat was given.
March 29, 1990	IND Safety Reports submitted (CS092006, ARR09290009; CS092010, ARR09290008; follow-up CS092011, ARR09289020).
April 4, 1990	IND Safety Report submitted (CS09201 I, ARR09290010).
April 5, 1990	FDA minutes of the February 7, 1990 meeting received.
April 11, 1990	Amendment concerning Clinical section submitted.
April 11, 1990	D. Jones called C. Schumaker regarding Nordic/Soviet protocols. Information has been forwarded to Dr. Kelsey. One item of the FDA minutes of the February 7, 1990 meeting clarified.

April 12, 1990	IND Safety Report submitted (ARR09290011, foreign).
April 18, 1990	Compassionate Use Request submitted.
April 27, 1990	IND Safety Report submitted (CS092006, ARR09290013; ARR09290012, foreign).
April 27, 1990	Protocol Amendments (CS092006,CS09201 I) submitted.
May 1, 1990	C. Schumaker called D. Brott regarding investigation of the credentials of an investigator previously submitted.
May 3, 1990	IND Safety Report submitted (CS092010, ARR09289028).
May 4, 1990	Annual progress report for the period of March 1, 1989 to February 28, 1990 (Serial No. 128) submitted.
May 1, 1990	IND Safety Report submitted (ARR09290014, foreign).
May 30, 1990	C. Schumaker called D. Jones regarding comments from Dr. Kelsey on Farmos Nordic/Soviet studies. Received by Dr. Justice but have not yet been reviewed.
June 5, 1990	Amendment concerning Clinical section submitted. Final study report CS092002.
June 5, 1990	IND Safety Report submitted (CS092006, ARR09290015).
June 7, 1990	C. Schumaker called D. Jones. A letter for Adria circulating within the division regarding Dr. Kelsey's comments on Nordic /Soviet studies.
June 11, 1990	IND Safety Report submitted (CS092010, ARR0929017; CS092011, ARR09290016).

June 11, 1990	E. Cutler (new CSO) called D. Jones. A question regarding packaging of tablets for stability conveyed to Dr. Sally Look, Reviewing Chemist.
June 15, 1990	S. Look called D. Jones. Packaging of tablets for stability discussed. Request regarding the packaging and the proposed stability protocol to be submitted in writing.
June 18, 1990	D. Hoberman called Brott and Harry. Issues regarding the statistical section of the revised Phase III protocols discussed. Written answers to be sent to the IND.
June 20, 1990	Letter to FDA submitting a copy of patient information booklet.
June 21, 1990	Brott/Harry called D. Hoberman. Unanswered questions from June 18, 1990 conversation discussed.
June 26, 1990	Brott/Shemano called E. Cutler regarding a compassionate use request.
June 27, 1990	New Protocol CS092018 submitted.
June 29, 1990	Amendment concerning addition of non-U.S.investigators submitted. Australian CS092011protocol submitted.
July 2, 1990	IND Safety Report submitted (CS092006, ARR09290021; Foreign ARR09290019, ARR09290020).
July 5, 1990	IND Safety Report submitted (CS092006, ARR09290022).
July 9, 1990	Compassionate Use Request submitted.

July 9, 1990	A letter from FDA to ADRIA submitting comments on IND and our correspondence of March 26, 1990. Comments pertaining to the acceptability of utilizing the Farmos Scandinavian and/or Soviet Phase III studies as adequate and well controlled studies.
July 10, 1990	United Kingdom CS092006 protocol submitted.
July 23, 1990	D. Brott called E. Cutler. The letter of July 9, 1990 regarding the Nordic/Soviet Phase III trials discussed.
July 26, 1990	Amendment concerning information in Clinical and Preclinical sections submitted.
July 27, 1990	D. Brott called E. Cutler regarding same issues as on July 23, 1990.
August 1, 1990	E. Cutler called D. Brott to request for a missing page from the July 9, 1990 compassionate use request. Checking on whether any comments on Phase III protocols.
August 3, 1990	Fax to FDA submitting the missing page from July 9, 1990 submission.
August 3, 1990	E. Cutler called D. Brott. No comments yet on Phase III protocols. Dr. Hoberman is on vacation.
August 8, 1990	IND Safety Reports submitted (CS092006, ARR09290023; Follow-up ARR09289004, ARR09289016, ARR09289017, ARR09289020; Follow-up ARR09290002).
August 8, 1990	South Africa CS092006 protocol submitted.
August 13, 1990	IND Safety Report submitted (CS092006, ARR09290024).

August 14, 1990	Amendment concerning Clinical section submitted. Updated Investigator's Brochure submitted.
August 23, 1990	D. Jones called Dr. Gurston Turner, Scientific Investigations. Acceptability of clinical data from South Africa discussed.
August 23, 1990	Fax from FDA submitting questions/ comments from Dr. Hoberman on Phase III protocols.
August 23, 1990	D. Brott called E. Cutler regarding transfer of a patient to another investigator.
August 28, 1990	IND Safety Reports submitted (CS092011, ARR09290025; CS092006, ARR09290028; ARR09290026, foreign).
August 29, 1990	IND Safety Report submitted (ARR09290027, foreign).
September 5, 1990	Letter from FDA submitting comments on protocol amendments submitted April 27, 1990.
September 19, 1990	E. Cutler called D. Jones to give information on stability studies after consulting with supervisory chemist.
October 1, 1990	IND Safety Report submitted (Follow-up CS092006, ARR09290023 and ARR09290028).
October 22, 1990	Amendment concerning Clinical section submitted (revised brochure, study report CS092003).
November 1, 1990	D. Brott called E. Cutler. According to Dr. Justice waivers per 21CFR 56.106 not necessary if non-U. S. sites comply with Declaration of Helsinki.
November 5, 1990	Amendment concerning Preclinical section submitted.

November 5, 1990	D. Brott called E. Cutler. Status of multicenter compassionate use protocol for desmoid tumor discussed.
November 15, 1990	IND Safety Report submitted (Foreign ARR09290033, ARR09290037, ARR09290041).
November 26, 1990	Letter to FDA submitting a response to questions/ comments in July 9, 1990 letter regarding Nordic/Soviet studies. Request for determination of acceptability of trials submitted.
November 30, 1990	IND Safety Report submitted (CS092011, ARR09290044).
November 30, 1990	E. Cutler called D. Brott. A change of tablet shape and whether bioequivalence study would be required discussed.
December 3, 1990	IND Safety Report submitted (CS092006, ARR09290043).
December 3, 1990	Protocol Amendment CS092006, CS092011 and response to statistical questions on Phase III protocol in September 5, 1990 letter submitted.
December 10, 1990	New Compassionate Use Protocol submitted.
December 11, 1990	Letter to FDA submitting investigator statements for Finland, Sweden and Norway; a status of carcinogenicity studies, and a request for discussion with pharmacologist.
December 12, 1990	D. Brott called E. Cutler regarding correction on Appendix to protocol.
December 13, 1990	Teleconference between Dr. Goheer, Dr. Taylor, E. Cutler, Dr. Imondi, and D. Brott regarding mouse and rat carcinogenicity studies.

December 14, 1990	E. Cutler called D. Brott. Carcinogenicity studies for adjuvant claim recommended.
December 17, 1990	Alterative dissolution method submitted (Serial 167).
December 26, 1990	E. Cutler called D. Jones. May proceed with desmoid tumor protocol.
January 8, 1991	D. Brott called E. Cutler requesting for status of response to Nordic/Soviet trial questions.
January 10, 1991	E. Cutler called D. Brott . Data from Nordic/Soviet trials will be acceptable to support an NDA.
January 23, 1991	IND Safety Report submitted (Follow-up CS092011, ARR09290044).
February 5, 1991	IND Safety Report submitted (CS092011, ARR09291001).
February 8, 1991	IND Safety Report submitted (CS092006, ARR09291002).
February 11, 199l	Letter from FDA notifying that division will accept Nordic and Soviet trial data in support of a new drug application.
February 11, 199l	Letter from FDA submitting questions and recommendations on protocol amendment submitted January 13, 1990.
February 22, 1991	IND Safety Report submitted (CS092006, ARR09291005).
March 4, 1991	Amendment concerning Clinical (BE study report for minor change in formulation), Preclinical, Pharmacology, Pharmacokinetic, and Toxicology sections submitted.
March 4, 1991	Canada protocol CS092006 submitted.

April 16, 1991	Letter to FDA submitting a response to questions/ comments received February 11, 1991 on Phase III protocol.
April 26, 1991	Annual Progress Report for the period of March 1, 1990 to February 28, 1991 submitted.
April 29, 1991	IND Safety Report submitted (CS092011, ARR09291008).
May 9, 1991	IND Safety Report submitted (CS092006, ARR09291010).
May 10, 1991	Request for Orphan Drug Designation submitted.
May 14, 1991	Protocol Amendment concerning CS092006 United Kingdom and South Africa and CS092011 Australia submitted.
May 17, 1991	Peter Vicary, Orphan Drugs called D. Jones. FDA now requiring applications to be formatted in accordance with the proposed regulations. Other issues regarding the application discussed.
June 13, 1991	R. Watson called P. Vicary regarding status of reformatting/ changes to orphan drug application.
June 19, 1991	Reformatted Request for Orphan Drug Designation submitted.
July 9, 1991	IND Safety Report submitted (CS092006, ARR09291016).
July 12, 1991	R. Watson called E. Cutler regarding the status of an amendment concerning alternative dissolution method.
July 16, 1991	D. Jones called E. Cutler regarding the compassionate use request.

July 17, 1991	IND Safety Report submitted (CS092006, ARR09291016).
July 27, 1991	Letter from FDA submitting an acknowledgement of receipt of the application for orphan drug designation.
August 2, 1991	Letter to FDA submitting a plan to amend Phase III protocols (add Part II, dropping high dose arm, to provide second study for NDA).
August 6, 1991	Amendment concerning Clinical section submitted. Final report CS092010 submitted.
August 15, 1991	IND Safety Report submitted (Follow-up CS092006, ARR09290024).
August 22, 1991	Amendment concerning CMC stability submitted.
August 27, 1991	R. Watson called E. Cutler regarding correction of AE number on one page of follow-up to safety report submitted August 15, 1991.
September 6, 1991	IND Safety Report submitted (CS092006, ARR09291021).
September 12, 1991	Jones/Watson called E. Cutler. A follow-up requested on status of amendment regarding dissolution method submitted December 17, 1990 (Ser. 167) and availability of comments on bioequivalency study report submitted March 4, 1991 (Ser.174).
September 16, 1991	R. Watson called P. Vaccari regarding inquiry on status of orphan drug petition; Dr. Haggerty currently reviewing.
September 19, 1991	Orphan Drug Designation for metastatic breast cancer submitted.

September 24, 1991	E. Cutler called D. Jones regarding response to follow-up request September 12, 1991: Revised dissolution method, another chemist to review, comments in two weeks; Bioequivalence study, PK reviewer indicated that the study would be reviewed as part of the NDA, (other background discussed) marketed dosage form will be revised formulation.
October 11, 1991	IND Safety Report submitted (CS092011, ARR09291024).
October 21, 1991	IND Safety Report submitted (ARR09291025, foreign).
October 29, 1991	IND Safety Report submitted (CS092011, ARR09291026).
November 1, 1991	IND Safety Report submitted (ARR09291028, foreign).
November 21, 1991	Protocol Amendments submitted (CS092006, CS092011, CS092006 South Africa, CS092011 Australia).
November 25, 1991	Letter from FDA. FDA finds Bioequivalency study submitted in March 4, 1991 amendment showing formulations to be equivalent.
November 27, 1991	Amendment concerning Clinical section submitted. Revised final study report CS092002.
December 5, 1991	D. Jones called E. Cutler . Suggested meeting to discuss results of interim analyses of Phase III studies, timing of NDA submission, and plans for second U.S.-based Phase III study; current Division policy on scheduling meetings discussed.
December 11, 1991	R. Watson called E. Cutler . A follow-up requested on status of information amendment for revised dissolution method (submitted December 17, 1990). Dr. Look has it on a priority list.

December 12, 1991	FDA authorized to cross reference IND on behalf of FARMOS who will study the effects of toremifene on multiple drug resistance.
December 20, 1991	E. Cutler called R. Watson. Verified that investigator submitted December 10, 1991 was participating in the desmoid tumor protocol.
December 30, 1991	R. Watson called E. Cutler. Part II of U.S. Phase III studies beginning; selected foreign sites which will meet same requirements as ongoing Nordic/Soviet sites regarding ethical considerations may be added; advised by Ms. Cutler to inform FDA of plans so that reviewer can be made aware.
January 7, 1992	Jones/Watson called E. Cutler regarding follow-up on revised dissolution method. Ms. Cutler sent to Biopharm for expedited review; reviewer in India until end of month.
January 14, 1992	E. Cutler called D. Jones. Questions regarding investigator's multiple drug resistance IND answered.
January 17, 1992	IND Safety Reports submitted (Foreign ARR09292001, ARR09292002, ARR09292003, ARR09292004).
January 30, 1992	R. Watson called E. Cutler regarding the follow-up requested on revised dissolution method.
January 30, 1992	E. Cutler called R. Watson. Biopharm reviewer's initial reaction to revised dissolution method was the higher rpm may be a problem, formal review expected in week or so; revised Phase III protocols submitted November 21, 1991 will not be sent for review until revised statistical section is submitted as indicated in cover letter.

February 7, 1992	E. Cutler called R. Watson. Revised dissolution method should be changed to 50 rpm instead of 75 rpm according to FDA reviewer.
February 14, 1992	IND Safety Report submitted (CS092011, ARR09292009).
March 19, 1992	R. Watson called E. Cutler. Phase III protocol amendments currently in review.
March 19, 1992	IND Safety Report submitted (Foreign ARR09292010).
March 24, 1992	R. Watson called E. Cutler. Request to treat a child on Desmoid Tumor protocol discussed; request to be faxed.
March 24, 1992	Fax to E. Cutler from R. Watson submitting a request from investigator to treat patient on Desmoid Tumor protocol by exception.
March 24, 1992	E. Cutler called R. Watson. Medical reviewer wanted to know what dose would be used for the child and to verify that evaluations would be done per protocol.
March 25, 1992	E. Cutler called R. Watson. Dosing and schedule for desmoid tumor patient agreed upon.
April 6, 1992	Protocol Amendments submitted (CS092006, CS092011, CS092006 South Africa, CS092011 Australia and updated Investigator Brochure).
April 16, 1992	IND Safety Report submitted (Foreign ARR09292011).
April 23, 1992	Amendment concerning CMC section submitted. Revised dissolution method submitted.
April 27, 1992	Amendment concerning CMC section submitted (Stability).

April 27, 1992	Letter from FDA regarding division policy on CVs as part of credentials.
April 29, 1992	Annual progress report for the period of March 1, 1991 to February 29, 1992 submitted.
June 23, 1992	Letter to FDA submitting investigator qualification statements (response to division policy change).
July 7, 1992	IND Safety Report submitted (CS092006, ARR09292015).
July 13, 1992	Letter to FDA submitting a revised investigator qualification statements.
July 24, 1992	Protocol Amendment concerning CS 092006 Canada submitted.
August 18, 1992	E. Cutler called R. Watson. Information requested regarding filing of NDA, for division planning purposes.
September 3, 1992	Fax to E. Cutler submitting a compassionate use request.
September 10, 1992	IND Safety Report submitted (ARR09292009 Follow-up).
September 15, 1992	Amendment concerning Clinical section submitted (Revised investigator's brochure).
September 23, 1992	IND Safety Reports submitted (CS092006, ARR09292021, CS092025, ARR09292022).
September 24, 1992	IND Safety Report submitted (CS092006, ARR09292020, also faxed).

September 25, 1992	Fax to E. Cutler from D. Jones. Request for scheduling conference call to discuss data cutoff for analyses for final reports.
September 29, 1992	R. Watson called E. Cutler regarding follow-up on three day safety report and division policy on AR reports; E. Cutler recommended scheduling meeting to discuss NDA in response to September 25, 1992 telefax.
October 5, 1992	D. Jones called E. Cutler referencing Dr. Burke's letter of June 22, 1992 concerning the use of tumor specific symptoms relating to toremifene.
October 8, 1992	Letter to FDA submitting a list of tumor specific symptoms for assessing effects of treatment on quality of life submitted for comment.
October 9, 1992	IND Safety Report submitted (CS092006, ARR09292023).
October 19, 1992	R. Watson called E. Cutler. Response status sought to October 8, 1992 letter regarding tumor specific symptoms. Informed Ms. Cutler of planned submission of background package and request to meet with Division. Information on changes to Investigator's Brochure (IB) will be sent as requested previously by Medical reviewer.
October 21, 1992	Letter to FDA submitting revisions to IB.
October 23, 1992	R. Watson called E. Cutler regarding the compassionate use request. Information faxed. Return telephone call approved request. Medical reviewer wants information on another patient treated at that institution.
October 27, 1992	IND Safety Report submitted (CS092006, ARR09292024).
October 30, 1992	Letter form ADRIA, Robert S. Watson to FDA requesting the Pre-NDA meeting. (Serial No. 233)

October 30, 1992	Background package (Efficacy) submitted and a request to meet with Division.
November 5, 1992	Information on patient requested October 23, 1992 submitted.
November 6, 1992	Letter from FDA submitting a response to October 8, 1992 letter.
November 12, 1992	IND Safety Report submitted (CS092006, ARR09291006).
November 13, 1992	IND Safety Report submitted (Follow-up ARR09292023, 09292024).
November 16, 1992	Authorization for Dr. Kent Osborne to cross reference our IND.
November 30, 1992	E. Cutler called R. Watson. Statement on cover letters for credentials discussed. Meeting with Division set for January 12, 1993.
December 9, 1992	D. Jones sent a telefax to E. Cutler regarding question for pharmacologist.
December 15, 1992	Additional background package for January 12, 1993 meeting submitted.
December 18, 1992	IND Safety Report submitted (Follow-up ARR09292022).
December 21, 1992	Teleconference between D. Jones, R. Watson and E. Cutler regarding question for pharmacologist (December 9, 1992 telefax). Answer expected in January. Details of the January 12, 1993 meeting discussed.

January 5, 1993	Letter from FDA (N.A.M. Atiqur Rahman) to Adria in response to the request of the company to discuss the NDA issues.
January 12, 1993	FDA meeting (ADRIA/FDA) regarding Pre-NDA clinical and preclinical issues. Results of Phase III studies discussed.
January 26, 1993	Minutes of the January 12, 1993 FDA meeting submitted.
January 27, 1993	Amendment concerning Preclinical section submitted.
February 2, 1993	Fax from R. Watson to E. Cutler request for a meeting.
February 3, 1993	Letter requesting meeting to discuss final study report sent.
February 4, 1993	Fax from E. Cutler to D. Jones submitting FDA's minutes of January 12, 1993 meeting.
February 8, 1993	Amendment concerning Clinical section submitted.
February 19, 1993	Background information package (copies of protocol and CRFs) submitted for March 4, 1993 meeting with FDA.
February 25, 1993	IND Safety Report submitted (for ARR09293003).
March 4, 1993	Meeting with FDA.
March 8, 1993	E. Cutler called R. Watson. Dr. Tolgyesi had questions regarding the formulation to be used in Dr. Osborne's study, conducted under his IND.

March 8, 1993	Fax to E. Cutler from R. Watson submitting a response to request for information in regards to the new formulation of Toremifene 60 mg tablets supplied by Farmos.
March 17, 1993	Telephone communication between A. Imondi and Dr. Goheer regarding neonatal studies in mice. Not required for either advanced or adjuvant indication, but Goheer advises that we do it as it could be very helpful to us.
March 19, 1993	Minutes of the March 4, 1993 FDA meeting submitted.
March 22, 1993	E. Cutler called R. Watson requesting for information on carcinogenicity studies to assist in review of Osborne's IND.
March 22, 1993	Fax to E. Cutler submitting a response to the above request.
March 23, 1993	Teleconference between Jones, Watson, Imondi and Dr. DeGeorge regarding carcinogenicity studies.
March 25, 1993	E. Cutler called R. Watson. Osborne will be placed on clinical hold pending review of carcinogenicity studies.
March 31, 1993	Amendment (Serial No. 252) describing the formulation that will be used by Farmos for Dr. Osborne's IND study submitted. Confirmation of formulation faxed to FDA on March 8, 1993.
March 31, 1993	Amendment concerning CMC section submitted.
April 2, 1993	D. Jones called G. Turner, FDA. Source documents in Soviet study discussed.

April 7, 1993	Adria regulatory department contacted the FDA and consulted the acceptability of radiology summary reports being sufficient as source documents when the x-ray or scans are missing. (Russia).
April 7, 1993	Teleconference between Jones, Watson and E. Cutler regarding how to submit interim reports of pivotal studies in NDA. Package inserts in foreign languages discussed.
April 8, 1993	IND Safety Report submitted (for ARR093293006).
April 14, 1993	Amendment concerning CMC section submitted.
April 14, 1993	Teleconference between Jones, Watson and E. Cutler. Submission of data on desmoid tumor discussed.
April 16, 1993	Amendment concerning Clinical section (Interim reports Phase III studies) submitted.
April 20, 1993	Desmoid tumor data submitted.
April 21, 1993	Compassionate use request submitted.
April 27, 1993	Amendment concerning Preclinical section (Two year carcinogenicity rats, mice) submitted.
April 30, 1993	IND Safety Report submitted (ARR09292022, second follow-up).
May 5, 1993	R. Watson called E. Cutler. 75 foreign reports received for the NDA will not be submitted to the IND at this time.
May 12, 1993	Amendment concerning Clinical and Preclinical sections submitted.

May 18, 1993	Letter to FDA requesting for pre-NDA meeting.
May 18, 1993	IND Safety Report submitted (ARR09293015).
May 25, 1993	E. Cutler called R. Watson proposing meeting dates and informing that desmoid tumor response not yet available, and that toxicology can be submitted early as a complete section. Clinical hold on Dr. Osborne's IND will continue.
May 26, 1993	E. Cutler called R. Watson. Meeting scheduled for June 30, 1993.
June 4, 1993	Annual progress report for the period of March 1, 1992 to February 28, 1993 submitted.
June 8, 1993	Dr. Goheer, FDA pharmacologist, called Watson requesting for additional desk copy of carcinogenecity reports. FDA meeting with National Center for Toxicology Research (NCTR) to discuss studies.
June 8, 1993	Additional desk copy of two volumes of carcinogenicity reports submitted as requested by Dr. Goheer.
June 10, 1993	E. Cutler called R. Watson requesting desk copies of other volumes of carcinogenicity reports, which will be used by NCTR for review. Osborne's clinical hold will continue. E. Cutler requests that meeting with FDA to discuss these issues not to be scheduled until NCTR review is complete.
June 10, 1993	Desk copies of requested volumes submitted.
June 11, 1993	IND Safety Report submitted (for ARR09293016).

June 21, 1993	R. Watson called E. Cutler. Status of responses to Dr. Osborne regarding clinical hold and to Adria regarding desmoid tumor sought. Letters will be mailed.
June 25, 1993	Letter from FDA informing that based on review of carcinogenicity data, the clinical experience with toremifene is insufficient to allow for its use in humans with benign proliferative breast disease. FDA recommends that mechanism of carcinogenesis be identified and show that it is not relevant to human use.
June 25, 1993	Letter form FDA to ADRIA to informing that IND 29,799 is on clinical hold.
June 25, 1993	Response to review of desmoid tumor information and answers to questions submitted.
June 28, 1993	Letter from FDA (N.A.M. Atiqur Rahman, Pharmacokinetic Evaluation Branch) regarding Pre-NDA meeting submission (May 18, 1993) to D Azarnoff.
June 30, 1993	Meeting with FDA . Draft table of contents and patient profiles discussed. Concentrated on clinical issues including section 6; also electronic submission.
July 8, 1993	Compassionate Use Request faxed to FDA. Approval faxed to Adria with stipulations for consent form.
July 16, 1993	Minutes of the June 30, 1993 meeting with FDA faxed to E. Cutler.
July 16, 1993	Teleconference requested to discuss the letter of June 25, 1993 regarding carcinogenicity studies.
July 19, 1993	IND Safety Report submitted (ARR09293018).

July 20, 1993	E. Cutler called D. Waters regarding dates proposed for teleconference. Request that minutes of FDA meeting fo June 20, 1993 be submitted to IND.
July 22, 1993	Minutes of the June 30, 1993 FDA meeting submitted.
July 23, 1993	Teleconference scheduled for August 12.
August 10, 1993	IND Safety Report submitted (ARR 09293018 follow-up).
August 10, 1993	Memo from A. Imondi with points for discussion during teleconference faxed to CSO.
August 10, 1993	Orion-Farmos submitted FDA a statement for Environmental Assesment (EA) section concerning waste and pollution control procedures.
August 12, 1993	Teleconference with pharmacology staff included DeGeorge, Goheer, Catlett, Cutler and Imondi, Gerber, Watson.
August 16, 1993	Amendment concerning Clinical section (Investigator's Brochure) submitted.
August 17, 1993	R. Watson called E. Cutler. Carcinogenicity data on disk not yet available for submission to Biometrics. Submission of sample case tabulations discussed.
August 18, 1993	By-variable listings formats submitted to FDA for review as agreed upon at the June 30, 1993 meeting.
August 20, 1993	Protocol Amendment (Nos. 7 and 8 CS092006, CS092011, CS092006 South Africa) submitted.

August 25, 1993	Telephone communication between Canales, Watson and Peter Smith, Foreign Inspections Branch regarding preapproval inspections and validation.
August 26, 1993	Amendment concerning Preclinical section (Reproductive study reports) submitted.
August 26, 1993	Information to support the dose selection in the rat carcinogenicity study submitted per August 12, 1993 teleconference submitted.
September 2, 1993	R. Watson called E. Cutler. Carcinogenicity data on disk should arrive September 10.
September 3, 1993	Type I GMF 3271 Oulu plant and Type II DMF 6652 for Toremifene Citrate submitted to FDA by Fermion.
September 3, 1993	J. Catlett called R. Watson regarding questions on by-variable listings. Bryan, Schoenfelder, and Souder joined Watson for discussion.
September 9, 1993	Telefax from FDA submitting a response to the August 18, 1993 letter regarding by-variable listings.
September 10, 1993	Orion-Farmos submitted an Authorization Letter to FDA for DMF Type I No 5144.
September 10, 1993	Letter to FDA (Dr. Lin in Biometrics) informing that carcinogenicity data submitted on disks.
September 20, 1993	R. Watson called E. Cutler. Status of carcinogenicity reports review sought.
September 21, 1993	IND Safety Report submitted (ARR09293025).

September 22, 1993	Information by Dr Desmond Thio (ADRIA) to Orion-Farmos of "Orphan Drug" status in Desmoid Tumors.
September 22, 1993	IND Safety Reports submitted (Foreign ARR 09293021, 09392022, 09293023).
September 23, 1993	R. Watson spoke to E. Cutler at ODAC meeting. Review of carcinogenicity reports ongoing; will continue to follow.
October 13, 1993	Dr. Wenjen Chen, Biometrics, called R. Watson regarding questions on carcinogenicity data on disk; answered by T. Robbins.
October 20, 1993	Dr. Chen called T.Robbins several times regarding carcinogenicity data.
October 26, 1993	R. Watson called E. Cutler. Status of reviews of carcinogenicity data discussed.
November 30, 1993	Letter from Orion Corporation /Fermion (L. Hildén) to FDA with updated new Drug Master File Type II No 6652 for Toremifene Citrate.
December 20, 1993	Authorization given for Dr. Samuels to cross reference our IND.
December 28, 1993	IND Safety Reports submitted (ARR09293029, ARR09293030).
April 29, 1994	Annual Progress report (Serial No. 290) for the period March 1, 1993 to February 28, 1994 submitted.
May 4, 1994	Orion Corporation gives Power of Attorney to Dan Azarnoff regarding IND and NDA applications of Toremifene tablet.

May 24, 1994	Authorization letter from Fermion to FDA regarding Type I DMF 3271 for Oulu plant and Type II DMF 6652 for Toremifene Citrate.
June 13, 1994	Telephone conversation between FDA and Dan Azarnoff regarding follow-up of status of Pre-NDA meeting.
June 16, 1994	Fax from FDA to D. Azarnoff requesting more info of documentation to be submitted for Pre-NDA meeting.
July 1, 1994	D. Azarnoff called M. Pelosi of FDA consulting the upcoming meeting (August 31, 1994).
July 5, 1994	Letter from D. Azarnoff to FDA /M. Pelosi.
July 18, 1994	D. Azarnoff contacted M. Pelosi: Notice of Pre-NDA meeting scheduled for August 23, 1994.
July 21, 1994	Authorization from PCI to FDA to refer to their DMF Type I No. 1876.
August 1, 1994	Authorization from Wheaton Plastic Products to FDA to refer to their DMF Type I 1466.
August 2, 1994	Authorization from Anchor Hocking Packaging Co. to FDA to refer to their DMF Type I No. 8260.
August 4, 1994	Authorization from Phillips Chemical Company to FDA to refer to their DMF Type I No. 1016.
August 5, 1994	Authorization from Chevron Chemical Company to FDA to refer to their DMF Type I No. 1646.
August 12, 1994	Authorization from Owens-Illinois Closure Inc. to FDA to refer to their DMF TypeI No. 2229.

August 31, 1994	Pre-NDA meeting at the FDA.
September 22, 1994	Letter from Orion Corporation to FDA / Gregory Burke informing of transfer of ownership of the IND 29,799 from Pharmacia Inc. to Orion Corporation, the U.S. agent being D. Azarnoff.
September 23, 1994	Letter from Orion Corporation to FDA /Center for Drugs and Biologics (Thomas J McGinnis) giving authorization to the FDA to refer to the DMF Type I for Turku Plant No. 5144.
September 26, 1994	Letter from Orion-Farmos to FDA indicating transfer of ownership of two orphan drug designations for toremifene.
September 27, 1994	D. Azarnoff contacted by telephone Maureen Pelosi of FDA. Determining number of copies of the pre-NDA submission.
October 6, 1994	Letter from FDA regarding the transfer of ownership of IND 29,799.
October 14, 1994	Dan Azarnoff submitted information to FDA requested by Maureen Pelosi, CSO, regarding the responsibilities of the new owner of IND 29,799.
October 17, 1994	Authorization from American White Cross to FDA. Authorization Letter to DMF No. 4164.
November 14, 1994	Letter from FDA (Gregory Burke) to D. Azarnoff referring to IND submitted as well as transfer of the IND from Pharmacia to Orion Corporation.
December 5, 1994	D.Azarnoff sent to FDA Sections 3,4 and 5 of a New Drug Application.

December 6, 1994	FDA/M. Pelosi called Orion Corporation / Antti Seppälä regarding a question concerning the NDA assigned number and when the rest of the file will be submitted. Information of CSO job to be transferred to Linda McCollum.
December 12, 1994	User Fee Identication Number ID No. 2705 assigned by FDA.
December 19, 1994	D. Azarnoff accompanying letter to FDA (Division of Oncology and Pulmonary Drug Products) submitting the NDA sections 1, 2, 6, 8, 10, 12 and 13 (14). Section 11 already submitted in electronic form December 14, 1994. Sections 3, 4 and 5 were previously submitted December 5, 1994.
January 3, 1995	Dr. Gerston Turner/ FDA/ Scientific Investigation Division called to request for a copy of the summary.
January 3, 1995	FDA / Linda McCollum called to request for a copy of the User Fee transmittal form.
January 4, 1995	Dan Azarnoff sent letter to FDA forwarding a Desk Copy of Vol 2.8 of the Clinical Data Section of the NDA.
January 4, 1995	Orion Corporation sent a fax to Linda McCollum of FDA with copies of the User Fee.
January 10, 1995	FDA/Division of Information System Design (HFD-70) asked whether the NDA will be submitted as a Computer Aided New Drug Application (CANDA).
January 10, 1995	Letter from D. Azarnoff to FDA/CDER notifying the intent to provide CANDA.
January 23, 1995	D. Azarnoff sent a letter to FDA submitting a response to a M Pelosi's request to update 1572s (Serial No. 302).

February 3, 1995	Letter from FDA to Orion Corporation (D. Azarnoff) acknowledging the receipt of submission of NDA. NDA 20-497 assigned to FARESTON®. Confirmation of receipt of the fees and application accepted on January 3, 1995.
February 16, 1995	McCollum of FDA contacted D. Azarnoff to request for pharmacological-toxicological information.
February 17, 1995	FDA/Linda McCollum requested for pharmacokinetic (PK) information.
February 22, 1995	Letter from D. Azarnoff to FDA (Linda McCollum) informing of time table submitting the reply to pharmacokinetic reviewer's request of February 17, 1995.
February 22, 1995	Two telephone calls from FDA to D. Azarnoff requesting additional three copies of volumes 2.38 and more information regarding question 6.
February 22, 19	D. Azarnoff called Linda McCollum regarding the time table for data and answers to the questions raised by the pharmacokinetic reviewer.
February 23, 1995	Request from FDA regarding pharmacokinetic data.
February 28, 1995	Clare Gnecco from FDA called Jouni Vuorinen and wanted some clarification on the coding system of study sites and investigators for the three pivotal studies. J. Vuorinen faxed the info.
February 29, 1995	Clare Gnecco from FDA called and confirmed the receipt of the coding list.
March 6, 1995	D. Azarnoff faxed to FDA (McCollum) information regarding questions 2 and 6 in FDA's fax dated February 17, 1995.

March 8, 1995	D. Azarnoff called McCollum (FDA) requesting status update for two studies requested by February 16, 1995 and a telephone conference.
March 8, 1995	Linda McCollum called D. Azarnoff informing about a meeting for the NDA status update for April 12, 1995.
March 9, 1995	Linda McCollum called D. Azarnoff informing that she will be the only one at the April 12th meeting.
April 5, 1995	D. Azarnoff called Dr. Burke of FDA giving answers to pharmacokinetic information requested by L. McCollum.
April 12, 1995	D. Azarnoff and A. Seppälä visit Linda MCCollum at FDA.
April 27, 1995	Letter from Dr. Margret A. Smithers of FDA to H. Rantala of Orion Corporation giving information on the postponing of the investigation at Orion Corporation.
May 7, 1995	Response to queries (fax dated February 17, 1995) submitted.
May 19, 1995	Annual Report submitted to FDA.
June 8, 1995	D. Azarnoff called McCollum of FDA submitting information regarding the final report on the oral toremifene rat teratology study.
June 20, 1995	D. Azarnoff called Dr. Hoiberg of FDA regarding the 120 Day Safety Update for NDA 20-497.
July 7, 1995	D. Azarnoff called McCollum summarizing the current status of the NDA.
July 10, 1995	Response to question 4 of the FDA request of February 23, 1995 submitted.

August 21, 1995	Questions 1-4 submitted from FDA/Dr. Brower and Martin.
August 21, 1995	NDA Safety Update Reports submitted.
August 22, 1995	Questions 1-3 submitted from FDA/Dr. Brower.
August 24, 1995	D. Azarnoff called A. Sigfried regarding information on ODAC/FDA meeting.
August 24, 1995	D. Azarnoff called McCollum who informed that she had received the committee's report.
August 25 - 30, 1995	FDA Inspection at Turku Plant.
August 30, 1995	FDA/G.Turner called D. Azarnoff to inform of audit of the clinical studies performed in St. Petersburg.
August 30, 1995	Rebeca Rodriquez/FDA sent Inspectional Observations (form FDA 483) to Heimo Rantala.
August 31, 1995	Telephone conversation between D. Azarnoff and Dr. Turner of FDA determining possible change of audit to St. Petersburg.
September 8, 1995	Statement regarding final report segment II study submitted.
September 17, 1995	Submission of ODAC briefing books.
September 18, 1995	Briefing book ODAC meeting.
September 19, 1995	CDER Dr. Alison Martin of FDA had questions concerning Safety Update (sent August 21, 1995).
September 19, 1995	Questions from FDA regarding several items in the NDA.

September 22, 1995	Response to FDA regarding queries of August 21, 1993 and September 19, 1995 submitted.
September 25, 1995	Orion submitted FDA with a Paradox disc containing St. Petersburg clinical data base.
September 26, 1995	Request from Dr. Martin/FDA concerning clinical data.
September 26, 1995	Ms. Adele Seifried of FDA called D. Azarnoff checking the conflict of interest items for the ODAC meeting: relationships between Orion, Adria and Pharmacia.
September 27, 1995	Dr. A. Martin of FDA sent a memorandum to D. Azarnoff requesting clarification for the "eight preselected and solicited events".
September 27, 1995	Responses submitted to Dr. Martin's queries of September 26 and 27, 1995.
September 28, 1995	A list of members attending the ODAC meeting submitted to Orion from FDA.
September 29, 1995	Protocol concerning St. Petersburg trial site submitted to FDA.
September 29, 1995	Dr. Turner of FDA called D. Azarnoff regarding data received for St. Petersburg audit. Invitation to be requested from St. Petersburg.
September 30, 1995	Electronic submission of carcinogenicity and toxicology reports.
October 2, 1995	N.N. Petrov Research Institute's invitation letter to FDA / Dr. Turner and Mr. Flynn.

October 2, 1995	Letter from FDA (Alan B. Lisook) to Orion Corporation informing of change of Dr. Garcia from principal investigator to subinvestigator status.
October 3, 1995	Response to Dr. Martin's questions of September 27, 1995 submitted.
October 3, 1995	Updated survial table of Erbamont I study submitted.
October 4, 1995	Response to Dr. Martin's questions of September 19 and 27, 1995 submitted.
October 5, 1995	FDA submitted biostatistical and medical review to Orion.
October 11, 1995	Draft questions for ODAC meeting submitted.
October 11, 1995	List of Orion personnel attending the ODAC meeting submitted.
October 11, 1995	Response request from FDA concerning definition of tumor response in Japanese trial.
October 16, 1995	ODAC meeting.
October 19, 1995	Submission of Erbamont I protocol and line listing of adverse events for sites 5, 34 and 37.
October 20, 1995	Faxed responses to telephone queries of October 19, 1995.
October 23, 1995	Oral Teratology Study in the Rat (segment II) submitted.
October 30, 1995	Response to Dr. Turner's request for a clarification concerning studies in Russia.

November 8, 1995	Letter from Dr. Lisook regarding Dr. Garcia's qualification.
November 20-24, 1995	FDA audit at the site N.N. Petrov Research Institute of Oncology, St Petersburg, Russia.
November 22, 1995	Response Dr. Turner request for 92006-023 adverse event line time printout and address of principal investigator.
November 27, 1995	Fax to Dr. A. Martin regarding Dr. Lisook's letter of October 25, 1995.
November 30, 1995	Response to Dr. Lisook regarding his letter of October 25, 1995.
November 30, 1995	Desk Copy of two toxicology reports and a floppy disk submitted.
November 30, 1995	English translations of Russian toxicological studies submitted to FDA.
December 3, 1995	Instructions for reading carcinogenicity bioassay disk data submitted.
December 13, 1995	Instructions for reading floppy disks submitted.
December 13, 1995	Letter from FDA to H. Rantala. Information on the review of the inspection of the manufacturing facility by R. Rodriguez.
December 14, 1995	Facsimile from FDA (Linda McCollum) to D. Azarnoff regarding deficiencies on the original submission of NDA 20-497 (environmental assessment, pharmacology/ toxicology).

December 18, 1995	Facsimile transmission from FDA to D. Azarnoff regarding Chemistry, Manufacturing, and Controls deficiencies on the original submission of NDA 20-497.
December 28, 1995	Desk Copy 12/28/95 submission to FDA.
December 28, 1995	D. Azarnoff's letter to FDA / Robert J DeLap submitting a response to pharmacology/toxicology reviewer's questions.
January 3, 1996	Letter from FDA to D. Azarnoff regarding the NDA submission. Amendments to the submissions of January 3, April 7, June 20, October 23, and November 30, 1995 acknowledged. Approvable Letter.
January 5, 1996	D. Azarnoff's letter to FDA to inform of our intention to reply to the Approvable letter of January 3, 1996.
January 23, 1996	Orion Corporation / T. Karhunsaari contacted FDA/Barbara Scherer and was told that FDA inspection Site # 92006-023, the study director of which is Dr. Levine, Baltimore, MD, has been inspected and no errors were found. Form FDA 483 was left at the site.
February 2, 1996	Fax from Orion Corporation to D. Azarnoff informing of shipment of pharmacology/toxicology replies to deficiencies dated December 14, 1995.
February 6, 1996	Authorization from PCI to FDA to refer to their DMF.
February 16, 1996	FDA bill number 961189 to Orion Corporation.
February 23, 1996	Dr. Wood informed about DMF deficiencies.

February 23, 1996	D. Azarnoff sent draft labeling to FDA.
February 26-March 1, 1996	FDA inspection concerning bioequivalence of a new formulation of toremifene 60 mg tablets.
February 27, 1996	Amendment to the initial cleaning validation protocol dated October 4, 1995.
February 29, 1996	Form FDA 483 Inspectional Observations concerning the inspection of February 26 - March 1, 1996.
March 1, 1996	A cheque (bill number 961189) submitted to FDA.
March 14, 1996	Orion Corporation's response to observations of the form FDA 483 dated February 29,
March 29, 1996	Adverse Drug Event (ADE) concerning subject 412601 submitted to FDA.
May 2, 1996	D. Azarnoff's letter to FDA Dr. DeLap: 1) response to January 3, 1996 approvable letter; 2) stability study report.
May 17, 1996	Labeling for 60 mg tablet bottles.
May 22, 1996	Revised table, Page 528 (labeling) submitted to FDA.
May 24, 1996	A letter from FDA/Dr. Brower to D. Azarnoff concerning our response of May 2, 1996 and containing an additional request regarding labeling.
June 5, 1996	Professional Information brochure (PIB) submitted to FDA.
June 7, 1996	Responses to Pharmacology/Toxicology queries of May 24, 1996 submitted.
June 12, 1996	A copy of the advertising material submitted to FDA.

June 12, 1996	Labels for 30 and 100 tablet bottles sumbitted.
July 19, 1996	Dr. Brower's review and queries concerning our response of May 2, 1996.
July 31, 1996	Linda McCollum of FDA sent a facsimile to D. Azarnoff concerning deficiencies in the EA review due to amendment dated May 2, 1996.
August 8, 1996	Orion's response to FDA concerning the EA review.
August 8, 1996	Desk Copy 8/8/96 submission.
August 12, 1996	Orion's response to FDA's Pharmacology/Toxicology queries of the letter dated July 31, 1996.
August 16, 1996	Orion's response to FDA concerning query D2 of approvable letter of January 3, 1996.
August 19, 1996	Letter to FDA asking for an inspection report.
August 20, 1996	FDA/Dr. Brower's comments on the August 12, 1996 submission.
August 27, 1996	Response to Dr. Brower's query of August 20, 1996.
August 30, 1996	Query from Biopharms reviewer.
September 4, 1996	Response to the August 30, 1996 Biopharm query.
September 6, 1996	D. Azarnoff called Linda McCollum about the FDA meeting of September 6, 1996.
September 19, 1996	D. Azarnoff called Linda McCollum, who confirmed the FDA review schedule.

September 23, 1996	Word Perfect disk containing information on labeling submitted to FDA.
September 25, 1996	D. Azarnoff called Linda McCollum : a request for a floppy disk with a copy of the June 5, 1996 PIB.
September 27, 1996	Response to FDA/DDMAC concerning the approval for blister label.
September 27, 1996	D. Azarnoff's letter to FDA Dr. DeLap submitting a response to the telephone query of September 25,1996.
September 30, 1996	FDA sent the inspection report regarding the FDA inspection of February 26 - March 1, 1996.
October 4, 1996	Desk Copy 10/4/96 submission.
October 9, 1996	Fax query from FDA, Linda McCollum concerning Pharmacology/Toxicology impurities listing.
October 10, 1996	D. Azarnoff called Linda McCollum giving the answer to the fax query October 9, 1996.
October 17, 1996	D. Azarnoff called McCollum regarding the FDA internal meeting of October 16, 1996.
October 17, 1996	Fax from McCollum : Pharmacology/Toxicology reviewer requests for information.
October 23, 1996	Response to the October 17, 1996 request submitted.
October 24, 1996	D. Azarnoff's letter to FDA Dr. DeLap: response to the fax query.

October 24, 1996	D. Azarnoff called McCollum regarding the response to the fax query.
October 31, 1996	NDA 20-497 FDA Approvable Letter.
November 1, 1996	D. Azarnoff's letter to FDA Dr. DeLap telling that Orion will file an amendment containing revised labeling and the request in the approvable letter of October 31, 1996.
November 8, 1996	Request compassionate use for Dr. Campos.
November 12, 1996	A telefax from FDA to Fermion concerning deficiencies in DMF.
November 14, 1996	D. Azarnoff's letter to FDA Dr. DeLap requesting a meeting related to the approvable letter of October 31,1996.
November 18, 1996	D. Azarnoff's letter to FDA Dr. DeLap: 1) adverse event report; 2) compassionate use, FM Serial No. 316.
November 29, 1996	D. Azarnoff's letter to FDA Dr. DeLap submitting three copies of a draft answer to question B.8 of approvable letter of October 31,1996.
December 13, 1996	Draft labeling for the December 19, 1996 meeting.
December 19, 1996	PIB/labeling meeting with FDA.
December 20, 1996	CMC meeting with FDA.
January 9, 1997	M. Tuominen/Fermion submitted a response to FDA regarding DMF type II No. 6652 for Toremifene Citrate. Amendment as response to Deficiencies, Final Version.

January 10, 1997	D. Azarnoff called Linda McCollum requesting the minutes of the December 20, 1996 meeting.
January 13, 1997	D. Azarnoff's letter to FDA Dr. DeLap: 1) adverse event report; 2) revised 1572s Serial No. 317.
January 15, 1997	Revised labeling submitted.
January 15, 1997	D. Azarnoff's letter to FDA Dr. DeLap submitting draft answers to approvable letter of October 31,1996.
January 22, 1997	D. Azarnoff's letter to FDA Dr. DeLap submitting three copies of final responses to the approvable letter of October 31,1996.
January 22, 1997	Response to queries of the December 20, 1996 meeting.
January 24, 1997	Adverse Drug Event (ADE) submitted to FDA.
February 5, 1997	Reply to B8 query of the approvable letter dated October 31, 1996.
February 25, 1997	Minutes of the meeting of December 20, 1996 submitted to FDA.
March 3, 1997	Validation package submitted.
March 19, 1997	Fermion's reply to the approvable letter dated October 31, 1996 concerning deficiencies in DMF.
April 7, 1997	FDA minutes of the December 20, 1996 meeting.

April 7, 1997	Revised specification for 60 mg tablet and label for 30 tablet bottle submitted.
April 18, 1997	Annual Report submitted to FDA.
April 29, 1997	Advertising material submitted to FDA/DDMAC.
May 6, 1997	D. Azarnoff called Linda McCollum regarding FDA update from the CMS response.
May 6, 1997	Dr. Gurtler's responses to Dr. Martin's questions.
May 8, 1997	FDA/Chemistry comments concerning labeling submitted.
May 8, 1997	Response to the May 8, 1997 deficiency comments submitted.
May 10, 1997	Orion submitted to FDA a sample containing a starter kit and a holder.
May 29, 1997	The official approval letter of NDA 20-497 from FDA effective on this date.

Certification of Copies of Application Papers
Attachment G

PATENT

Attorney Docket No. _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,696,949)
)
Issued: September 29, 1987)
)
To: Reijo J. Toivola, Arto J. Karjalainen, Kauko O.)
A. Kurkela, Marja-Liisa Södervall, Lauri V. M.)
Kangas, Guillermo L. Blanco and Hannu K.)
Sundquist)
)
Assignee: ORION-YHTYMÄ OY)
)
For: NOVEL TRI-PHENYL ALKANE AND ALKENE)
DERIVATIVES AND THEIR PREPARATION)
AND USE)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

CERTIFICATION

I, RONALD J. KUBOVCIK, do hereby certify that this accompanying application for extension of the term of U.S. Patent 4,696,949 under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) duplicates thereof.

Respectfully submitted,

Dated: July 23, 1997

Ronald J. Kubovcik
Reg. No. 25,401

Declaration Pursuant to 37 C.F.R. §1.740(b)
Attachment H

PATENT
Attorney Docket No._____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,696,949)
)
Issued: September 29, 1987)
)
To: Reijo J. Toivola, Arto J. Karjalainen, Kauko O. A. Kurkela, Marja-Liisa Södervall, Lauri V. M. Kangas, Guillermo L. Blanco and Hannu K. Sundquist)
)
Assignee: ORION-YHTYMÄ OY)
)
For: NOVEL TRI-PHENYL ALKANE AND ALKENE DERIVATIVES AND THEIR PREPARATION AND USE)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 C.F.R. §1.740(b) ACCOMPANYING
APPLICATION UNDER 35 U.S.C. § 156 FOR EXTENSION OF PATENT TERM

I, RONALD J. KUBOVCIK, do hereby declare:

I am a patent attorney authorized to practice before the United States Patent and Trademark Office and have been appointed as attorney by the owner, ORION-YHTYMÄ OY, of U.S. Patent No. 4,696,949, with regard to this application for extension of the term of the patent under 35 U.S.C. §156.

I have reviewed and understand the contents of the application submitted herewith pursuant to 37 C.F.R. § 1.740.

I believe that the patent is subject to extension pursuant to § 1.710.

I believe that an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations.

I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in § 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Dated: July 23, 1997

Ronald J. Kubovcik
Reg. No. 25,401